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Original Communications

CORONARY ARTERY DISEASE IN MEN EIGHTEEN TO THIRTY-NINE YEARS OF AGE

Report of Eight Hundred Sixty-Six Cases, Four Hundred Fifty With Necropsy Examination*

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SYMPTOMATOLOGY OF THE "ACUTE ATTACK"

Symptoms of Onset.—The onset was practically always sudden and dramatic. Pain was the outstanding symptom of the "coronary attack." It was the commonest symptom both during the attack and at the onset of the attack, but it was not always the first symptom. Inasmuch as death was sudden or the patient was not seen by a physician until after death in many of the cases, the symptoms could not be ascertained in all. Altogether there were 208 of the 450 fatal cases in which the patient died so unexpectedly or in such circumstances that a history of the attack could not be obtained. Of the remaining 242 cases,

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pain was present in 236 and absent in 6. In the group of 400 patients who survived an attack of acute myocardial infarction, pain was the most noteworthy symptom in 396 cases. Therefore, of 642 cases in which a history could be elicited, pain was present in 632 patients (98 per cent). It was the primary or first symptom in 575 patients (90 per cent) but ensued rapidly in the other fifty-seven.

The primary symptoms of the onset of the attack are listed in Table XX. There it will be noted that manifestations of shock, such as weakness, sweating, pallor, and small, rapid pulse, were the next most common symptoms (17 per cent), and that these symptoms occurred naturally much more often in the group of fatal cases than in those patients who survived (37 per cent as compared with 5 per cent). Dyspnea occurred at the onset in 9 per cent of the patients, and nausea, vomiting, or both were present in 7 per cent. Other symptoms worthy of note were much less common.

Subsequent Symptoms.—As the attack progressed, symptoms other than the initial one rapidly ensued, but on the whole, the list is similar; in fact, several symptoms occurred almost simultaneously from the start in many cases. This accounts for the fact that in Table XX the percentage figures aggregate more than 100. For instance, among the fatal cases manifestations of shock were noted 313 times*; dyspnea and/or pulmonary congestion (râles) and/or cough in 159

TABLE XX. PRIMARY SYMPTOMS AT ONSET OF ACUTE ATTACK IN MEN 18 TO 39 YEARS OF AGE, INCLUSIVE, WITH CORONARY DISEASE

SYMPTOMS	FATAL CASES*		SURVIVORS		TOTAL	
	NO.	%†	NO.	%†	NO.	%†
Pain	236	97.5	339	84.8	575	89.6
Manifestation of collapse or shock	90	37.2	19	4.8	109	17.0
Dyspnea	20	8.3	37	9.3	57	8.9
Nausea, vomiting, or both	25	10.3	17	4.3	42	6.5
Indigestion	13	5.4	3	0.8	16	2.5
Syncope	4	1.7	7	1.8	11	1.7
Dizziness	6	2.5	4	1.0	10	1.6
Palpitation of heart	1	0.4	4	1.0	5	0.8
Congestive failure	5	2.1	0	0.0	5	0.8
Convulsions	4	1.7	0	0.0	4	0.6
Nervousness or psychic depression	2	0.8	2	0.5	4	0.6
Diarrhea	3	1.2	0	0.0	3	0.5
Hemiplegia	3	1.2	0	0.0	3	0.5
Choking	0	0.0	2	0.5	2	0.3
Delirium	1	0.4	0	0.0	1	0.2
Anorexia	1	0.4	0	0.0	1	0.2
Numbness in arms			1	0.3	1	0.2
Total patients with symptoms	242		400		642	

*Of the 450 patients, 208 either died too soon to be questioned or their history was unknown.

†Percentages are based on total number of patients with symptoms. This and the fact that there may have been more than one primary symptom account for the fact that the percentage figures aggregate more than 100.

*This figure represents the sum of symptoms considered manifestations of shock, namely, sweating, weakness, collapse, pallor, cyanosis, and a sensation of heat.

patients; nausea, vomiting, or both in ninety-nine; restlessness, nervousness, or apprehension in twenty-seven; unconsciousness in twenty-seven, convulsions in twenty-five, "indigestion" in thirteen, congestive failure in ten, and diarrhea (a noteworthy symptom) in eight patients. Among the survivors, individual symptoms of shock were noted 436 times, but physicians considered only thirty patients to be in "shock." In this group also there were dyspnea and/or pulmonary congestion (râles) and/or cough in 216 patients; nausea, vomiting, or both in 134; restlessness, nervousness, or apprehension in ninety-two; unconsciousness in forty-five, convulsions in none, "indigestion" in thirty-three, congestive failure in none, and diarrhea in seven. Other symptoms, as shown in Table XXI, were choking, anorexia, constipation, dizziness, mental dullness, chills, headache, palpitation, numbness of one or both arms, thirst, desire to

TABLE XXI. SUMMARY OF MAIN SYMPTOMS OF THE "ATTACK"* IN MEN 18 TO 39 YEARS OF AGE, INCLUSIVE, WITH CORONARY DISEASE

SYMPTOMS	FATAL CASES		SURVIVORS		TOTAL	
	NO.	%	NO.	%	NO.	%
Pain	236	97.5	396	99.0	632	98.4
Weakness (Symptoms of Shock)	89	36.8	123	30.8	212	33.0
Collapse (Symptoms of Shock)	152	62.8	41	10.3	193	30.1
Sweating (Symptoms of Shock)	13	5.4	148	37.0	161	25.1
Cyanosis (Symptoms of Shock)	45	18.6	46	11.5	91	14.2
Pallor (Symptoms of Shock)	11	4.5	58	14.5	69	10.7
Heat† (Symptoms of Shock)	3	1.2	20	5.0	23	3.6
Dyspnea, cough, râles	159	65.7	216‡	54.0	375	58.4
Nausea, vomiting, or both	99	40.9	134	33.5	233	36.3
Nervous manifestations§	27	11.2	92	23.0	119	18.5
Unconsciousness	27	11.2	45	11.3	72	11.2
Numbness‖	10	4.1	59	14.8	69	10.7
Indigestion¶	13	5.4	33	8.3	46	7.2
Dizziness	10	4.1	29	7.3	39	6.1
Palpitation	1	0.4	33	8.3	34	5.3
Convulsions	25	10.3	0	0.0	25	3.9
Choking or gagging	9	3.7	16	4.0	25	3.9
Anorexia	1	0.4	16	4.0	17	2.6
Headache	0	0.0	15	3.8	15	2.3
Diarrhea	8	3.3	6	1.5	14	2.2
Congestive failure	10	4.1	0	0.0	10	1.6
Hemiplegia	3	1.2	2	0.5	5	0.8
Chills	4	1.7	0	0.0	4	0.6
Constipation	1	0.4	3	0.8	4	0.6
Thirst	2	0.8	0	0.0	2	0.3
Tympanites	2	0.8	0	0.0	2	0.3
Delirium	1	0.4	0	0.0	1	0.2
Desire to defecate	1	0.4	0	0.0	1	0.2

*By "attack" is meant the acute manifestations of onset of coronary insufficiency, with or without acute coronary artery occlusion.

†By "heat" is meant a subjective sensation of body warmth.

‡This figure includes twenty-two cases of orthopnea and twenty-one cases with cough, five with bloody sputum.

§"Nervous manifestations" includes restlessness, nervousness, anxiety, apprehension, fear of death, psychic depression, and mental dullness.

‖"Numbness" refers to a feeling of numbness in shoulders, arms, hands, fingers, and legs.

¶"Indigestion" usually means a sensation of fullness or of a lump in the epigastrium without actual pain.

defecate, swelling of the abdomen, and hemiplegia. The difference between the two groups may be accounted for on the basis of duration and severity, the men surviving naturally having milder manifestations on the whole.

The most difficult symptoms to tabulate and evaluate were those which might be attributed to shock. In the group of survivors, 148 had sweating; 123, weakness or tiredness; fifty-eight, pallor; forty-six, cyanosis; forty-one, collapse; and twenty, a subjective sensation of heat; but in only thirty were the combinations such that the physician designated the state of the patient as one of "shock." The inadequacy of observations and records of many different physicians make these figures inaccurate, but still they indicate a trend.

Pains.—The various locations in which the prominent symptom of pain in the fatal group occurred are shown in Table XXII. The division of anterior thoracic pain into precordial and substernal is admittedly inaccurate. Many of the instances of precordial pain were probably mainly substernal. Because of the radiation from the primary site, usually the anterior thoracic region, there were two or more sites in fifty-two cases. Pain did not radiate in 184 patients, a feature worthy of note. In the eight patients in whom it occurred in the back it had usually radiated from the front. Anterior myocardial infarcts were found in five of these patients.

TABLE XXII. LOCATION OF PAIN IN FATAL CASES OF CORONARY DISEASE IN MEN 18 TO 39 YEARS OF AGE, INCLUSIVE

LOCATION		NUMBER
Thoracic (anterior)		178
Location not given*	77	
Precordial*	59	
Substernal	42	
Thoracic (posterior)		8
Abdominal		55
Location not given	18	
Epigastric	28	
"Stomach"	9	
Left shoulder and arm		23
Both shoulders and arms		10
Wrists		2
Fingers		1
Neck		5
Head		1
Calves of legs		1
Bones		1

*Many of these were probably substernal.

Descriptions of the character, severity, radiation, and duration of pain were naturally sketchy because so many of the patients were very ill. In four patients in whom the pain was adequately described, it was mild; in seventeen, moderate; and in eighty-four, severe. It was variously described as oppressive (thirteen), constricting (seven), numbing (four), burning (three), sharp (two), aching (two), tearing (one), dull (one), rheumatic (one), and as a soreness (one). In the cases of sudden death (minutes to hours) the duration of the pain was not

stated, but in twenty-eight cases in which the men lived longer than twenty-four hours the duration of the initial attack was given as follows: 1 to 5 minutes in three, 6 to 15 minutes in four, 16 to 30 minutes in one, 30 minutes to 4 hours in twelve, 5 to 12 hours in three, 1 day in one, 2 days in one, and 3 days in three.

Statements made by the men concerning factors which induced pain are not reliable, since in so many of the cases the pain "just developed." However, seventeen said it was induced by exertion; three, by rest; and five, by eating. Many of the men were given injections of morphine, but there are no accurate figures as to its effectiveness. The pain was relieved by rest in four cases, by drinking water in two, spontaneously in two, and by the use of nitroglycerin in one.

More exact were the data concerning pain in the 400 cases of the survivors. Pain was the outstanding symptom in 396 (99 per cent) of these. It occurred as the initial symptom in 339 and developed soon after the onset of the "attack" in fifty-seven more. In 220 patients the pain was described as constricting in fifty-three, oppressive in fifty, pressing in forty-eight, as a numbness in forty-two, sharp in thirty-seven, viselike in twenty-five, aching in twenty-two, knifelike in twenty, as a tightness in eighteen, crushing in thirteen, squeezing in thirteen, stabbing in twelve, burning in twelve, heavy in nine, sticking in eight, as a soreness in seven, cramplike in six, tearing in six, gripping in five, compressing in four, agonizing in four, as a sensation of a lump in four, boring in three, cutting in three, as a pounding in three, as smothering in three, as choking in two, and hammerlike, shocking, shooting, stinging, and throbbing in one each. In eighteen cases the pain was not described. These types of pain may be grouped as follows: (a) oppressive, pressing, crushing, heavy, compressing, smothering, and choking in 129 patients; (b) constricting, viselike, as a tightness, squeezing, and gripping in 114; (c) sharp, knifelike, stabbing, sticking, cramplike, tearing, cutting, shooting, and stinging in seventy-four; (d) aching, burning, as a soreness, and boring in forty-four; (e) numbness in forty-two; (f) pounding, hammerlike, and throbbing in five; (g) agonizing and shocking in five; and (h) as a lump in four.

So far as could be judged from the description, the pain was severe in 305 of the survivors, moderate in fifty-four, and mild in twenty-four. Of the remaining seventeen survivors, there was no pain in four and in thirteen the data were too meager to permit classification.

A striking feature of the pain in forty-one (approximately 10 per cent) of the survivors was exacerbation of the pain on deep breathing. In none of these patients was there evidence of pericarditis or pleurisy on physical or roentgenographic examination.

The substernal and left anterior thoracic areas were the most common sites of pain among the survivors. Pain was described as definitely substernal in 192 cases, as precordial in ninety-five cases, and as left anterior thoracic in thirty. Other locations were the epigastric region (twenty), the abdomen (four), the neck and throat (three), the mouth, teeth, and jaws (two), the legs only (two), and both arms, below the left scapula, the back between the shoulders, the left axilla, the left side of the chest posteriorly, the left elbow, the left shoulder,

the right shoulder, and the head (one, each). Forty patients stated that they had pain in the chest but did not localize it.

Among the 396 survivors who gave a history of pain, it was stated to have radiated to various parts of the body in 272 cases (69 per cent), proportionately many more than in the acutely fatal group. The patients described the radiation very accurately. In many cases the pain radiated to more than one part of the body. The various areas of radiation were as follows: left arm (ninety-nine), both arms (eighty-one), left shoulder (sixty-eight), neck (thirty-eight), shoulders (thirty-five), back (thirty-five), another part of the chest (twenty-two), to the precordium from the sternal region (twenty-two), mouth and jaws (twenty-one), to the sternal region from the precordium (fourteen), to the left side of the chest from the sternal region (eleven), right arm (ten), fingers (nine), wrists (eight), head and face (seven), abdomen (seven), elbows (six), right shoulder (six), left shoulder (six), left axilla (six), fingers of the left hand (six), right side of chest (five), left elbow (four), left hand (four), hands (three), legs (three), left wrist (two), axillae (two), right axilla (two), palate (two), nipple (one), and all extremities (one).

Among the survivors, the duration of pain during the acute attack was from a few seconds in one case to twenty-one days in another. The pain was considered to be continuous during the acute phase in 314 patients and intermittent in eighty-two. There was no apparent relationship between the duration of the pain and the subsequent clinical course. Ten seconds was recorded as the shortest duration of pain, and the patient in whom this duration was recorded experienced an otherwise typical clinical course with classical electrocardiographic changes, fever, leucocytosis, and increased sedimentation rate (see Case 71). On the other hand, the patient who had continuous substernal pain for twenty-one days described it as severe for forty-eight hours and then as a constant dull ache for the next nineteen days. In many instances the duration of pain was directly affected by the medication given, such as morphine or other analgesic drugs. In the group of 314 patients with continuous pain, twenty-five (8 per cent) had pain for less than one hour, ninety-five (30 per cent) for one to four hours, 136 (43 per cent) for four to twenty-four hours, thirty-one (10 per cent) for twenty-four to forty-eight hours, and twenty-seven (9 per cent) for more than forty-eight hours. In the group of eighty-two patients with intermittent pain, the pain lasted from a matter of seconds to five hours and recurred one or more times during the "acute coronary attack."

Clinical Course of the Fifty-four Patients Hospitalized for Twenty-four Hours or More Before Death.—Fifty-four of the soldiers who died were in a hospital twenty-four hours or more, and many of them were examined adequately. In six the course of the disease following the initial attack was asymptomatic and death occurred suddenly (Table XXIII). In fourteen cases the patients were improving and died unexpectedly. Recurrent pain of anginal type occurred in forty-five patients, with the number of attacks as listed in Table XXIII. Pain was present terminally in twenty-two patients. Congestive failure ensued in thirteen patients; this figure includes five patients in whom it had been present

for one to seven months before final hospitalization. Embolization occurred in five patients and convulsions, in six.

The course was typical of myocardial infarction in thirty-one patients, but in two of these no infarction was found; in one there was an organizing thrombus in the left anterior descending artery; in the other, sclerotic occlusion of the left anterior descending and right circumflex arteries. In the first of these, electrocardiograms showed typical anterior myocardial infarction; in the second, atypical anterior myocardial infarction.

TABLE XXIII. SYMPTOMS OF COURSE IN FIFTY-FOUR FATAL CASES—PATIENTS HOSPITALIZED BECAUSE OF CORONARY DISEASE

HOSPITAL COURSE	NUMBER*	
Asymptomatic with unexpected death		6
Improving but death unexpected		14
Recurrent pain of anginal type		46
1 attack	14	
2 attacks	7	
3 attacks	4	
4 attacks	3	
Numerous attacks	9	
Continuous	9	
Pain present terminally		22
Dyspnea		15
Congestive failure†		13
Pulmonary congestion		11
Convulsions		6
Shock		6
Embolization		5
Nausea and vomiting		4

*The total of this column of 148 means that some of the symptoms were combined in individual cases.

†Five had congestive failure prior to hospitalization; eight developed it during hospitalization.

The cardiac signs in these cases were not unusual. There were no abnormal findings in twenty-nine patients. The heart was enlarged in six; the heart sounds were distant in seven; a systolic murmur was heard in six, There were premature beats in five patients, tachycardia in five, and gallop rhythm in five. A pericardial friction rub was heard in only one patient. An aortic diastolic murmur was present in one patient. This was a case of syphilitic aortitis with complete occlusion of the orifice of the right coronary artery and almost complete occlusion of that of the left coronary artery. Other physical signs were those to be expected, such as pulmonary congestion, cyanosis, dyspnea, and edema.

The blood pressures were normal or low in all but twelve patients, in eight of whom the pressures were slightly elevated, in one, moderately elevated, and in three, high (200/120 to 224/129).

The temperature was above normal in thirty-two cases and remained elevated for a longer time than in the patients who recovered. However, the number of cases is not large enough to warrant emphasis of this point. In twenty-eight patients the temperature was less than 103°F. at the highest, ranging in most from 99 to 102° Fahrenheit. In three patients the highest reading was

from 103 to 105°F., and in one patient the temperature rose terminally to 108° Fahrenheit.

The sedimentation rate in this group of cases was of very little help. Fifteen patients had a normal rate; four, a slightly elevated rate; three, a moderately elevated rate; and four, a greatly increased rate. In the other patients the rate was not recorded.

Roentgenograms of the chest were made in most cases. The heart shadow was found to be enlarged in nineteen patients; evidence of pulmonary congestion or edema was noted in nine, and infarcts of the lungs were stated to be present in three patients. Pleural effusion was evidenced in two patients, thickened pleura in one, atypical pneumonia in one, and "pneumonitis" in one patient.

Electrocardiograms.—Electrocardiograms were made in only forty-nine of the entire series of 450 fatal cases, ten in cases in which death occurred within twenty-four hours and thirty-nine in cases in which the duration was more than twenty-four hours. The number of electrocardiograms made in individual cases varied from one to eleven. Table XXIV shows the time elapsing between the last electrocardiogram and death, the electrocardiographic findings or the interpretation of them, and the pathologic findings. This table speaks for itself and

TABLE XXIV. ELECTROCARDIOGRAPHIC DATA IN RELATION TO PATHOLOGIC FINDINGS IN FORTY-NINE PATIENTS WHO DIED OF CORONARY DISEASE

TIME MADE BEFORE DEATH	ELECTROCARDIOGRAPHIC DATA	PATHOLOGIC FINDINGS
	Cases in Which Death Occurred Within Twenty-four Hours	
Just before death	$S\text{-}T_2$ and $S\text{-}T_3$ depressed	Infarct 0.2 by 5 cm. in posterior wall of left ventricle involving septum with thrombosis of left circumflex artery
Day of death	Normal	Infarct 1.5 cm. in diameter in anterior one-third of septum with thrombosis of right coronary and left circumflex arteries
4 months	Not available	No infarction; sclerotic occlusion of left anterior descending artery with thrombosis
2 months	Inverted T in IV F	Infarct of left ventricle with sclerotic occlusion of left anterior descending, right circumflex, and left circumflex anterior arteries
8 months	QRS N-shaped; late inversion of T in CF_2, slight late inversion of T in CF_3	No infarction; sclerotic occlusion of left anterior descending artery with thrombosis
2 months	$S\text{-}T_2$ and $S\text{-}T_3$ inverted; Q_3 present	No infarction; sclerotic occlusion of all coronary arteries
1 month	Normal	No infarction; thrombus in left anterior descending artery
1 day	Atypical infarction	No infarction; sclerotic occlusion of left anterior descending and left circumflex arteries
Not recorded	4:1 heart block	Infarct 8 by 4 cm. in wall of left ventricle with thrombosis of left anterior descending artery
2 days	Normal	No infarction; sclerotic occlusion of right circumflex artery

TABLE XXIV. ELECTROCARDIOGRAPHIC DATA IN RELATION TO PATHOLOGIC FINDINGS IN FORTY-NINE PATIENTS WHO DIED OF CORONARY DISEASE—(CONTINUED)

TIME MADE BEFORE DEATH	ELECTROCARDIOGRAPHIC DATA	PATHOLOGIC FINDINGS
Cases in Which Patients Lived More Than Twenty-four Hours		
Days	Typical anterior infarction	Infarct of half of left ventricle and septum 5 by 3 cm. with sclerotic and thrombotic occlusion of left anterior descending artery
2 months	Typical anterior infarction	Infarct, massive, of left ventricle and septum with thrombus in left anterior descending artery
2 days	Typical anterior infarction	Infarct in anterior wall of left ventricle and septum with thrombus in left anterior descending artery and sclerotic occlusion of left circumflex artery
1 day	Typical anterior infarction	Infarct in apex of left ventricle anterior with thrombus in left anterior descending artery
20 days	Typical anterior infarction; right bundle branch block	No infarction; organizing thrombus in left anterior descending artery
2 months	Typical anterior infarction	Infarct 3 by 1 by 0.8 cm. in anterior portion of left ventricle and septum with thrombus in left anterior descending artery
Day of death	Typical anterior infarction	Infarct 2 cm. in diameter in left ventricle with thrombus in left anterior descending artery
21 days	Typical anterior infarction	Infarct 3 cm. in diameter in apex of left ventricle and septum with thrombus in left anterior descending artery
2½ months	Typical anterior infarction	Infarct in interventricular septum with sclerotic and thrombotic occlusion of left anterior descending artery
11 months	Typical anterior infarction	No infarction; simple narrowing of coronary arteries
Not recorded	Typical anterior infarction	Infarct of left ventricle and septum with thrombus in left anterior descending artery
2 days	Typical anterior infarction	Infarct 7.5 by 5.4 cm. in apex of left ventricle and septum with thrombus in left anterior descending artery
7 weeks	Typical anterior infarction	Infarct in apex of left ventricle; practically complete sclerotic occlusion of proximal third of all cornary arteries.
Day of death	Typical posterior infarction	Several infarcts left ventricle and right ventricle with thrombosis of right circumflex artery
2 months	Typical posterior infarction	No infarction; thrombotic occlusion of left anterior descending artery
6 days	Typical posterior infarction	Infarct 3 by 3 cm. in posterior wall of left ventricle and septum with thrombosis of right circumflex and left anterior descending arteries
1½ months	Atypical anterior infarction	Infarct in anterior wall of left ventricle with organized thrombus in left anterior descending artery
4 days	Atypical anterior infarction	No infarction; sclerotic occlusion of left anterior descending and right circumflex arteries
19 days	Atypical posterior infarction	No infarction; thrombosis of left anterior descending artery

TABLE XXIV. ELECTROCARDIOGRAPHIC DATA IN RELATION TO PATHOLOGIC FINDINGS IN FORTY-NINE PATIENTS WHO DIED OF CORONARY DISEASE—(CONTINUED)

TIME MADE	ELECTROCARDIOGRAPHIC DATA	PATHOLOGIC FINDINGS
1½ months	Anterior and posterior infarction	Infarct 2 by 4 cm. in anterior wall of left ventricle with sclerotic occlusion of left circumflex and right circumflex arteries
Not recorded	Anterior and posterior infarctions	Infarct 4 by 4 cm. in apex of left ventricle with thrombosis of left anterior descending artery
1 day	Anterior and posterior infarctions	Infarcts in apex of left ventricle, posterior basal portion of left ventricle, and right ventricle, with thrombosis of left anterior descending and right circumflex arteries
5½ months	Atypical infarction; defective intraventricular conduction	No infarction; simple narrowing of coronary arteries
1 day	Atypical infarction; right bundle branch block; auricular flutter	No infarction; sclerotic occlusion of left anterior descending artery
4 days	Myocardial damage	Infarct in anterior wall of left ventricle with thrombosis of left anterior descending artery
2 days	Myocardial damage	Infarct 3 cm. in diameter in anterior wall of left ventricle with thrombosis of left anterior descending artery
2½ months	Myocardial damage	Infarcts in left and right ventricles with sclerotic occlusion of left anterior descending and right circumflex arteries
2 days	Myocardial damage	Infarcts in posterior wall of left ventricle and septum with simple narrowing of coronary arteries
1½ months	Myocardial damage	No infarction; sclerotic occlusion of left anterior descending artery
2 days	Myocardial damage	No infarction; thrombosis of left anterior descending artery
23 days	Myocardial damage	No infarction; sclerotic occlusion of left anterior descending artery
13 days	Myocardial damage	No infarction; sclerotic occlusion of left anterior descending artery
8 days	Myocardial damage	No infarction; sclerotic occlusion of left circumflex artery
2 months	Myocardial damage	No infarction; sclerotic occlusion of left anterior descending and right circumflex arteries with fresh thrombosis of the former
4 days	Myocardial damage	Infarct in posterior wall of left ventricle and septum with thrombosis of all three major arteries
10 days	Myocardial damage	Infarct in wall of left ventricle with sclerotic occlusion of left anterior descending and right circumflex arteries
Not recorded	Myocardial damage	Infarct 4 by 6 cm. in anterior wall of left ventricle with sclerotic occlusion of left anterior descending and left circumflex arteries
3 months	Myocardial damage	Old massive infarct in anterior wall of left ventricle and septum with old thrombotic occlusion of left anterior descending artery
3 days	Normal	No infarction; thrombosis of left anterior descending artery

shows the number of discrepancies, many of which might have been obviated had a greater number of precordial or V leads been used. It is notable that there were four normal electrocardiograms, made, respectively, one month, three days, and two days before death, and on the day of death. The first three were recorded in cases without infarctions but with complete occlusion of major coronary arteries, the fourth in a case with infarction and thrombosis of the right circumflex and left anterior descending arteries.

Clinical Diagnosis.—The clinical diagnosis was correct in 116 of the 450 fatal cases. The diagnosis was considered correct for practical purposes if coronary artery disease or any phase of it was given. The diagnoses were correct in eighty-three of the 375 cases in which death occurred within twenty-four hours and in thirty-three of the seventy-five cases in which the patient lived more than twenty-four hours. It must be noted, however, that in 247 of the cases of sudden death the patient expired before a medical officer saw him. Thus, there were 203 opportunities to make a diagnosis on living patients. The diagnostic accuracy is, therefore, 58 per cent.

Physical Examination of the Survivors.—The records of physical examinations made during or shortly after the acute attack were available in 388 of the 400 cases. In 185 (48 per cent) of the cases, an abnormality of the pulse was noted. The pulse rate was rapid (above 100 per minute) in ninety-one, slow (below 60 per minute) in sixty-four, and considered to be of poor quality or feeble in thirty patients. Arrhythmias were present in sixty-two additional patients (see cardiac findings). In all instances the pulse was considered to be normal in quality and rhythm after a period of hospitalization.

The cardiac findings were of considerable interest because of the large group of patients with entirely normal physical findings. In 231 (60 per cent) of the 388 cases, the physical examinations of the heart were recorded as entirely normal. The most frequently observed cardiac abnormality, that of poor heart sounds, described by various examiners as distant, feeble, weak, faint, and muffled, was found in seventy-two patients. Cardiac arrhythmias were noted in sixty-two patients; premature ventricular contractions were heard fifty-seven times, paroxysmal auricular tachycardia and auricular fibrillation, two times each, and auricular flutter, once. These arrhythmias were transient and ceased within twenty-four hours after hospitalization in every instance. Murmurs were heard in thirty-five patients during the initial examination; in thirty-three the murmurs were systolic and in two they were thought to be diastolic; in thirty-two patients these murmurs were heard over the mitral area, and in three, systolic murmurs were heard at the base. The murmurs were transient, none were considered characteristic of any definite valvular lesion, and all had disappeared before the patients were discharged from the Army hospitals. Gallop rhythms were heard in twenty patients during the first examinations; but no exact descriptions of the timing were available, and in only three instances did the gallop rhythm persist.

Several other abnormal cardiac findings were observed and are worthy of mention. Cardiac enlargement was thought to be present in sixteen patients.

Transient pericardial friction rubs were heard in eleven patients, and all of these disappeared within forty-eight hours. In seventeen additional patients a rub was heard later. Accentuated aortic second sounds were heard in seven patients and an accentuated pulmonic second sound in three. A tic-tac rhythm was recorded on three occasions.

Important abnormal pulmonary signs were noted in fifty-one individuals; râles were heard in forty-one patients, in four of whom frothy or bloody sputum was present. In twenty-one patients wheezing noises over the lungs were heard during the acute attack of myocardial infarction, and in most of these instances considerable coughing was observed during the physical examination.

Other important physical signs were noted during the initial physical examinations in Army hospitals. Sweating was noted in 109 patients, pallor in fifty-seven, cyanosis in forty-five, and definite clinical shock in twenty-nine. Seventeen patients were disorientated and confused or in a semiconscious state, and ten other patients groaned or appeared to be choking or suffocating during examination.

Signs of aging were present in forty-two of the men. Twenty-three men were reported as appearing definitely older than their stated ages; eleven others had gray hair; and eight had arcus senilis.

Blood Pressure Records of the Survivors.—There were records of the blood pressure readings both at induction and during the acute attack for 263 survivors. In 108 patients (41 per cent) the blood pressure at induction and the readings during the attack were entirely within the normal limits of 100 to 139 mm. Hg systolic and 60 to 89 mm. Hg diastolic.

Fifty-two patients (20 per cent) had definite elevations of the blood pressure above induction levels, the systolic being 140 mm. Hg or greater and the diastolic, 90 mm. Hg or higher. Thirty-three of these patients had normal pressures at induction, eight had elevated systolic and diastolic readings at induction, six had normal systolic pressures and borderline elevated diastolic pressures (90 or 92 mm. Hg) at induction, and five had elevated systolic and normal diastolic pressures at induction. Of the thirty-three patients with normal systolic and diastolic pressures at induction and elevated pressures during the attack, fifteen had systolic pressures ranging from 140 to 149 mm. Hg, eight from 150 to 159 mm. Hg, five from 160 to 169 mm. Hg, one from 170 to 179 mm. Hg, three from 180 to 189 mm. Hg, and one over 190 mm. of mercury. The last patient had a blood pressure of 118/76 at induction and a pressure of 190/90 during his acute attack. Of this group, the diastolic pressures were between 90 and 99 mm. Hg in sixteen, between 100 and 109 mm. Hg in twelve, and over 110 mm. Hg in five.

In eight patients in whom there occurred a definite rise in systolic and diastolic blood pressures during the "acute attack," as compared with the induction blood pressures, the systolic and diastolic blood pressures were slightly elevated at induction. The diastolic pressures ranged between 90 and 98 mm. of mercury. Of the eight men, four had systolic pressures of 150 and 159 mm. Hg in the acute attack, one between 160 and 169 mm. Hg, one between 170 and 179 mm. Hg, one between 180 and 189 mm. Hg, and one between 190 and 199

mm. of mercury. In the patient with the highest systolic pressure, the blood pressure was 144/96 at induction and 196/114 during the attack. A summary of the increase in the diastolic pressures showed two men to have diastolic pressures between 100 and 109 mm. Hg, four between 110 and 119 mm. Hg, and two of 120 mm. of mercury. The patient with the highest diastolic pressure had a pressure of 144/90 mm. Hg at induction and of 180/120 mm. Hg during the "acute coronary attack."

In six patients in whom there was a normal systolic pressure and a slightly elevated diastolic pressure of 90 to 92 mm. Hg at induction, there was a definite elevation of both systolic and diastolic pressures during the acute attack. In two instances the systolic elevation was between 140 and 149 mm. Hg; in two, between 150 and 159 mm. Hg; in one, 170 mm. Hg; and in the sixth case, 180 mm. of mercury. In the last patient the induction pressure was 130/90 mm. Hg, and the pressure during the attack was 180/110 mm. of mercury. In these six patients the diastolic pressures during the acute attack were, respectively, 96, 120, 100, 100, 110, and 110 mm. of mercury.

Five men who had normal diastolic pressures and slightly elevated systolic pressures on induction showed elevation of both systolic and diastolic pressures during the "acute attack." Two had systolic levels during the acute attack between 150 and 159 mm. Hg, two had levels of 160 mm. Hg, and one, a level of 230 mm. of mercury. The greatest change in this group occurred in a man whose induction pressure was 140/88 mm. Hg and whose pressure during the acute attack was 230/120 mm. of mercury. The diastolic pressures of these men during the acute attack were, respectively, 102, 108, 100, 120, and 120 mm. of mercury.

Twenty-four men showed definite elevation of either the systolic or the diastolic pressure during the acute attack, as compared with the blood pressure at induction. Eighteen soldiers showed an elevation of the diastolic pressure to 90 mm. Hg or higher, and six others had a systolic elevation to 140 mm. Hg or higher. Among the eighteen patients in whom there were diastolic elevations from previous levels to 90 mm. Hg or higher, fourteen had entirely normal induction blood pressures, four had systolic elevations at induction of 140 to 149 mm. Hg, and three had diastolic pressures at induction of 90 to 92 mm. of mercury. Of the eighteen soldiers with elevated diastolic pressures during the "acute coronary attack," nine had elevations from 90 to 99 mm. Hg, eight, from 100 to 109 mm. Hg, and in one the pressure reached 110 mm. of mercury.

In the six soldiers in whom there was an elevation of the systolic pressure alone, the induction blood pressures were normal in four, the systolic pressure 148 in one, and the diastolic pressure 90 mm. Hg in one. During the acute attack the systolic pressure was elevated in four to 140 to 149 mm. Hg, to 158 mm. Hg in one, and to 180 mm. Hg in another. The greatest change in this group was from 148/80 mm. Hg at induction to 180/80 mm. Hg during the acute attack.

Thirty-six men had a definite drop of blood pressure at the beginning of the "acute attack" as compared with induction pressure. In sixteen men the drop brought the systolic pressure to below 100 mm. of mercury. At induction, ten of this group had normal blood pressures, three had slightly elevated systolic and diastolic pressures, two had slightly elevated diastolic pressures, and one,

an elevated systolic pressure. During the early stage of the "acute attack," seven had systolic pressures between 90 and 99 mm. Hg, four between 80 and 89 mm. Hg, one between 70 and 79 mm. Hg, one between 50 and 59 mm. Hg, and three had practically imperceptible pressures. The diastolic pressures in this group also showed a relative drop. In fourteen patients the diastolic pressures were 60 mm. Hg or lower (in three, practically imperceptible) and in two the diastolic pressure was 70 mm. of mercury. In twenty of these thirty-six patients the systolic and diastolic pressures were within the normal range, whereas the pressures at induction were slightly elevated. The pressures in all but three of this group were between 140 and 149 mm. Hg, systolic, and about 90 mm. Hg, diastolic.

In twenty-nine patients there was a drop in the systolic pressure alone during the "acute attack." In nineteen of these the systolic drop was from 140 to 149 mm. Hg at induction to 100 to 139 mm. of mercury. In ten of them there was a definite drop of systolic pressures to a level below the 100 mm. Hg during the "acute attack," whereas the diastolic pressures remained within normal limits.

There were eight patients in whom there was a slight drop in the diastolic pressure during the "acute attack," as compared with the blood pressures at induction. In most of these the drop was very slight, from a borderline level of 90 to 93 mm. Hg to normal levels 10 to 20 mm. Hg lower, as follows: from 130/90 to 108/80, 108/90 to 110/80, 130/93 to 120/70, 112/85 to 100/56, 135/90 to 118/76, 130/90 to 110/70, 130/90 to 122/78, and from 132/92 to 100/50.

During the "acute attack" four men had a slight drop in the systolic pressure and a rise in the diastolic pressure, as compared with the pressures at induction, as follows: from 150/90 to 140/120, 150/90 to 140/96, 140/80 to 118/94, and from 150/90 to 136/120.

Two men had very slight systolic elevations and a slight diastolic drop during the "acute attack," as follows: from 128/90 to 140/84, and from 132/100 to 140/84.

The behavior of the blood pressure in these 263 patients during the "acute attack" may be summarized as follows:

	NUMBER	PER CENT
Remained the same	108	41.1
Systolic and diastolic rose	52	19.8
Systolic and diastolic dropped	36	13.7
Systolic alone rose	6	2.3
Systolic alone dropped	29	11.0
Diastolic alone rose	18	6.8
Diastolic alone dropped	8	3.0
Systolic dropped and diastolic rose	4	1.5
Systolic rose and diastolic dropped	2	0.8
	263	100.0

The subsequent course of the levels of the blood pressures was as follows: Blood pressure readings were available during the entire period of hospitalization for 255 of the 263 survivors who had blood pressure determinations made at the time of induction into the Army and during the acute "coronary attack." There were 179 (70 per cent) in whom the blood pressure remained normal or returned to normal levels within twenty-four hours after the initial hospitalization and continued normal throughout hospital treatment. In fifty-six men (22 per cent) in whom there was either an elevation or lowering of blood pressure readings from normal levels of 100 to 140 mm. Hg systolic and 60 to 90 mm. Hg diastolic during the "acute attack," normal levels were reached after a period of forty-eight hours or longer following the onset. Twenty patients (8 per cent) showed constantly elevated or lowered blood pressures during the period of convalescence following the acute "coronary attack"; eleven patients had "low" blood pressures and nine revealed varying degrees of arterial hypertension.

Among the 108 patients in whom there was no apparent change in the blood pressure levels found at induction and the levels observed during the acute attack, the levels remained normal throughout the entire convalescent period of eighty-five. In the same group the blood pressure levels in twenty patients fell below the normal range after the "attack" but returned to normal levels at varying times during convalescence. In these twenty patients with transient subnormal blood pressure levels the following time relations may be of interest. Two showed a drop of blood pressure twelve hours after the first normal blood pressure was noted in the "acute attack," and in both instances the blood pressure reached normal levels in three days. In seven patients the drop in blood pressure occurred twenty-four to forty-eight hours after the onset of the "attack" and remained at low levels for varying periods of time; in two, the pressures were low for one day, in two, for three days, in one, for four days, in one, for seven days, and in one the pressures were low for six weeks. In eleven soldiers the initial blood pressure drop occurred from four to six days after the onset and remained at low levels from periods varying from three days to six weeks before returning to normal. In two others the blood pressure dropped to subnormal levels within forty-eight hours after the onset of the attack and remained below normal throughout the remaining period of Army medical observation. In another patient an elevated blood pressure was noted on the eighth day after the "attack," and this elevation persisted.

In forty-nine of the fifty-two patients in whom there was definite elevation of the systolic and diastolic blood pressure during the acute "coronary attack," as compared with known previous blood pressure levels, frequent blood pressure determinations were available during convalescence. In thirty patients the elevated blood pressures returned to normal levels within twenty-four hours after the onset and remained normal; in eleven others normal blood pressure levels were reached at a longer period of time after the onset of the "attack." In this latter group of eleven men, normal levels were attained after forty-eight hours in six patients, after seventy-two hours in one, after ninety-six hours in two, after six days in one, and after six weeks in one patient. Three men showed an elevation of blood pressure levels during the acute "attack" and also through-

out the period of convalescence; two others experienced a drop of blood pressure to very low levels within twenty-four hours after the onset of the attack, and in each instance the blood pressure remained low. In three other soldiers the elevated pressure noted early in the acute phase of the attack dropped to very low levels for five to seven days before returning to a normal range.

Adequate follow-up blood pressure readings were available for analysis in all thirty-six patients who showed a drop in the systolic and diastolic blood pressures during the acute "coronary attacks." In twenty-three men the blood pressure returned to normal levels within twenty-four hours and remained normal throughout the long period of convalescence. In ten men the pressures ultimately returned to normal after a period of forty-eight hours or longer with low blood pressure levels; in three men the pressure returned to normal levels in forty-eight hours, in one man in five days, in one man in six days, in one man in eight days, in two men in three weeks, and in two men in six weeks. In the three remaining patients the low blood pressure noted during the acute "coronary attack" persisted throughout the entire period of hospitalization.

There were twenty-eight patients in whom blood pressure determinations were available following the acute "coronary attack" who, during the attack, showed a definite drop in the systolic blood pressure levels. In eighteen patients the blood pressures, both systolic and diastolic, were normal within twenty-four hours after the onset of the acute attack and remained normal throughout the remainder of hospitalization. Six soldiers showed normal blood pressure levels after forty-eight hours or longer of low systolic levels; in one man the pressure returned to normal in forty-eight hours, in two men in seventy-two hours, in one man in five days, in one man in thirteen days, and in one man in fourteen days. In two other patients the low systolic pressure remained below 100 mm. Hg throughout the period of hospitalization; and in two others, after forty-eight hours of low blood pressures a persistent hypertension developed.

Five of six patients with an elevated systolic and a normal diastolic blood pressure during the acute "coronary attack" within twenty-four hours had normal blood pressures that persisted throughout hospitalization. In the sixth patient the blood pressure remained elevated.

Follow-up blood pressure determinations were available in sixteen patients in whom there was an elevation of the diastolic blood pressure during the acute coronary attack. In eleven instances the diastolic pressure had returned to normal levels within twenty-four hours after the acute attack and remained normal throughout further hospitalization. In one instance the diastolic and systolic blood pressures dropped to below the normal range and remained low during hospitalization; in another the blood pressures at first returned to normal levels, and then both systolic and diastolic pressures became constantly elevated. In the three remaining patients of this group the diastolic blood pressure remained elevated for thirty-six to seventy-two hours and then returned to normal levels; in two of these patients an occasional drop in the systolic and diastolic blood pressures was observed between the third and eighth weeks of treatment.

The changes in blood pressure observed in conjunction with and following occlusion in this group of patients may be compared with the experience of others.

Levine and Brown[102] stated that the blood pressure occasionally remained high with occlusion, but the higher the blood pressure, the more marked was the fall of pressure in most cases. Allen[125] observed that the blood pressure usually fell within the first seventy-two hours but that this fall might be delayed in rare cases for ten days to two weeks. The pressure stayed down for more than a few hours, and if it had been 200 mm. Hg or more it went down to 110 to 120 and remained there for weeks; the prognosis had to be guarded until it assumed a higher level. It rarely returned to 200 mm. but generally rose to 150 to 175 and remained there, recovery usually being delayed until the blood pressure had reached its normal or nearly normal level. When blood pressure was above normal before the fall occurred the outlook was better than when it was within the normal range. Palmer[105] stated that changes in the blood pressure and the height of the blood pressure following recovery from an attack of coronary thrombosis were, on the whole, of little significance. Weiss[126] commented that although a fall in blood pressure has been given as one of the most important criteria for differentiating coronary artery occlusion from angina pectoris, a brief initial rise may occur in the former, and he reported three cases showing an early rise in pressure. He quoted Fishberg to the effect that shock or peripheral circulatory failure predominated in the first days of coronary thrombosis in individuals who had previously had slight symptoms or no symptoms of cardiac insufficiency and made the observation that in the initial stage of traumatic shock the arterial pressure may rise as a consequence of arteriolar constriction in the extremities before it falls. He also quoted Mendlowitz, Schauer, and Gloss, who suggested, on the basis of animal experiments, that for a brief period following coronary occlusion a peripheral vasoconstriction occurred to compensate for the coincident diminution in cardiac output. Master and associates[110] noted that occasionally the onset of coronary occlusion in patients with severe pain was associated with a transitory rise of blood pressure which sometimes reached 200 mm. of mercury. However, they stated that the pressure always fell during the attack, rapidly in 57 per cent and gradually in 42.5 per cent; occasionally a week or more elapsed before a significant fall became evident. The most rapid fall seemed to occur in nonhypertensive patients in whom the attack was fatal. The actual fall in pressure depended largely upon the initial level; 20 per cent who survived had an initial systolic pressure of 200 mm. Hg or more and the pressure did not fall below 150, and in the group with pressures of 150 to 190 mm. Hg, a fall below 150 mm. occurred in all but 3 per cent and below 100 mm. in 30 per cent. The diastolic pressure followed the same trend as the systolic, but the drop was less precipitate and less marked. Chambers[111] found that in 63 per cent of 100 cases of infarction there was an initial fall of blood pressure, in 32 per cent no change, and in 5 per cent an initial rise. All of the patients in the last group had hypertension and of these only one survived. The fall in blood pressure usually remained within hypertensive levels and it was immediate or delayed as long as seven days. They regarded an early return to normal or preocclusional levels as a good prognostic sign; the blood pressure usually did not return to former levels in the fatal group. The number of survivors regaining hypertension after the occlusion increased with time; 58 per cent had done so by the second year. After

recovery the height of the blood pressure had no effect on the frequency of recurrence of infarction or ultimate prognosis. All of the articles quoted included observations on both male and female patients.

DISCUSSION OF SYMPTOMATOLOGY

Reference to the literature on the symptomatology of coronary artery disease with acute occlusion shows, as is generally known, that pain is the commonest and most prominent symptom of the attack. For instance, in Howard's[46] series of 165 cases, pain occurred in 93 per cent; Kennedy[127] reported pain to be absent in only 4 per cent of 200 cases, with so-called classical pain in 91 per cent of the cases of recent infarction; Bean[128] found pain to be present in 75 per cent of 104 first attacks and 66 per cent of forty second attacks; Herrmann and Dechard[129] recorded pain in ninety-five of 127 cases; Babey[130] found pain to be absent in only one of 116 cases; Pollard and Harvill[71] reported 375 cases, in 353 of which pain was present; Rosenbaum and Levine[131] found pain to be absent in only 3 per cent of 208 cases, and Kugel[83] saw less than 3 per cent of 350 cases without pain. On the other hand, much has been written on the subject of painless coronary occlusion. Thus, Davis[132] found pain to be absent in twenty-nine of seventy-six cases, and in these the onset was abrupt with dyspnea. Other authors have noted that pain is likely to be absent in patients in whom dyspnea is a prominent symptom or in whom congestive failure is present.[1,92,129,133,134] However, as pointed out by Bean,[128] pain and congestive failure are not mutually exclusive; and Smith and associates[135] stated that sooner or later pain and dyspnea are commonly combined.

Hammon[136] observed that the pain of acute coronary artery occlusion is more circumscribed than the pain of angina pectoris; we doubt, however, whether this holds true sufficiently often to be helpful. Descriptions in the literature of the nature of the pain are similar to those given in our series. It appears also that radiation of the pain is not so common as is generally believed. For instance, among Nathanson's[34] 113 cases the pain radiated from the sternal, precordial, or epigastric region in only 10 per cent, and in Bean's[128] 300 cases there was no radiation in seventy.

Willius[60] emphasized the occurrence of anginal pain before the attack. It was present in eighty-three of 370 cases two weeks to fifteen years before the acute occlusion and persisted or appeared after occlusion in 167 cases; it was present before occlusion in twenty-seven in which it did not recur after occlusion. Previous angina was present in forty-two of Bean's[128] 300 cases. Smith, Sauls, and Ballew[75] reported angina both before and after occlusion in thirty-three of 100 cases; only before the attack in thirteen cases, and only after the attack in twenty-three cases. Fisher and Zukerman[137] noted previous angina in forty-five of 108 cases.

The subject of premonitory or preliminary pain has been discussed by Feil,[138] Sampson and Eliaser,[66] Master and associates,[119] and others. There is no way of knowing, however, when such pains are the precursor of acute myocardial infarction. The whole matter is tied in with the differentiation of

classical angina and so-called attacks of coronary insufficiency. If angina of effort, which began insidiously, has become established in a patient, one may feel relatively safe in assuming that the angina does not forbode an attack of myocardial infarction, although the possibility of infarction in such cases is always present. On the other hand, isolated attacks of anginoid pain, particularly when not induced by exertion and when accompanied by sweating, should always be considered of serious import and the patient treated as if an acute myocardial infarction were imminent. These are the cases in which the question of whether to use Dicumarol is important; it is probably more important to use it in such cases than in those in which the diagnosis of acute myocardial infarction has been made. An objection to its use, however, is that the likelihood of intimal hemorrhage might be increased, This we are inclined to doubt.

The prominence of epigastric pain has been noted repeatedly. It is merely a variant of substernal pain. Nathanson[34] reported epigastric pain in 25 per cent of 113 cases; Howard,[46] in 13.3 per cent of 165 cases; Bean,[128] in twenty-nine of 300 cases; Smith and associates,[75] in fifty of 100 cases; and Fisher and Zukerman,[137] in eight of 108 cases.

The foregoing data from the literature were based on series of patients of all ages. Goodson and Willius,[68] in a report of thirty patients under 40 years of age, noted a preceding anginal syndrome (one day to six months) in eight. Three of these patients experienced no pain with the attack.

Dyspnea, the symptom of the attack which we observed next most commonly, appears also to be the next most common one in published series of cases. It is probably due to some degree of left ventricular failure and is often confused with the pain, in that a feeling of suffocation may be interpreted either as pain or as difficulty in breathing. Hammon[136] stated that dyspnea is seldom absent, Wolff and White[1] reported dyspnea in almost all of twenty-three cases. Parkinson and Bedford[40] found that dyspnea and failure without pain characterized one of their clinical groups based on eighty-three cases, the other two being sudden death and prolonged anginal pain with shock. Of Howard's[46] 165 patients, sixty-four had dyspnea. In the series of 420 cases studied by Smith and co-workers,[135] dyspnea was present in 189 and paroxysmal dyspnea in thirty-five. Rosenbaum and Levine[131] reported dyspnea in 71 per cent of 208 cases. In fifty-nine of 108 cases reviewed by Fisher and Zukerman,[137] there was dyspnea; in five, orthopnea; in two, persistent cough; and in one, hemoptysis. In Bean's[128] comprehensive study of 300 cases, dyspnea was present before the attack in eighty-five; paroxysmal nocturnal dyspnea, in thirty; and orthopnea, in forty-seven. In the first coronary attack 95 per cent of patients had dyspnea, 68 per cent had orthopnea, and 24 per cent had Cheyne-Stokes breathing; in the second attack 96 per cent had dyspnea, 63 per cent had orthopnea, and 71 per cent had Cheyne-Stokes respiration. In reviewing the past history of 235 cases of coronary thrombosis, Phipps[139] found that twenty-one patients had only dyspnea and seventeen had paroxysmal nocturnal dyspnea, while forty-seven had "myocardosis, a symptom-complex of dyspnea, palpitation and precordial discomfort or pain." He stated, "Dyspnea, otherwise unexplained, and marked on slight exertion in a middle-aged individual, is more than suggestive of underlying coronary disease."

Various authors have commented on nervous manifestations. Wolff and White[1] stated that restlessness is characteristic. Syncope and convulsions have been noted. Cookson[140] found syncope or epileptiform attacks in fifteen of 200 cases. Herrmann and Dechard[129] reported syncope in five of 127 cases.

Vasomotor symptoms and/or shock are common. The highest percentages reported were by Rosenbaum and Levine[131]; among 208 cases, shock was present in 54 per cent, and cyanosis, in one-half of the cases; sweating also was common. Hammon[136] noted that blanching and sweating are common and that transient sweating is sometimes observed.

Gastrointestinal symptoms are also common. Parkinson and Bedford[40] found vomiting to be usual after the onset and sometimes repeated for days. Howard[46] reported vomiting in 28 per cent of his cases; Bean,[128] in 59 per cent in both first and second attacks. A few other authors found much smaller percentages of vomiting. Phipps[139] noted previous indigestion in nineteen of 235 cases. Hammon[136] observed that epigastric pain was often associated with tenderness and rigidity, nausea, and vomiting; in such cases differential diagnosis may be difficult. Diarrhea was noted by some authors.

We have selected Bean's[128] data from 300 cases with autopsy as most comparable with ours. His figures on the symptomatology are as follows:

SYMPTOMS PRIOR TO THE INITIAL INFARCT (125 CASES OF BEAN'S SERIES)

	NUMBER OF CASES	%
Dyspnea or exertion	88	70
Weakness	67	54
Cough	51	41
Nocturia	50	40
Orthopnea	47	38
Ankle edema	44	35
Angina pectoris	42	34
"Indigestion"	35	28
Paroxysmal nocturnal dyspnea	30	24
Palpitation	30	24
Syncope, fainting spells	28	22
Users of digitalis	18	14
Hemiplegia	11	9
Users of nitroglycerin	9	7
Auricular fibrillation	2	2

Painful prodromal symptoms appeared twenty-eight times. They were observed only twice before a second infarction and in no subsequent attacks.

SYMPTOMS OF THE ACUTE ATTACK IN BEAN'S SERIES

	FIRST ATTACK		SECOND ATTACK	
	NUMBER OF CASES	%	NUMBER OF CASES	%
Dyspnea	114	95	67	96
Enlarged heart	72	83	53	85
Weak heart sounds	77	85	56	82
Râles	91	83	54	82
Cyanosis	69	77	44	86
Cough	32	70	27	84
Pallor	38	69	26	79
Pain	104	75	40	66
Orthopnea	66	68	37	63
Sweating	31	60	15	60
Vomiting	47	59	16	59
Ankle edema	58	55	32	54
"Shock"	79	57	34	45
Restlessness	50	44	37	49
Tachycardia (rate over 108)	43	42	32	48
Systolic murmur	38	38	24	39
Cheyne-Stokes respiration	25	24	25	71
Ascites	11	26	14	42
Cloudy sensorium	41	26	16	33
Enlarged liver	11	18	7	23
Gallop rhythm	12	12	11	27
Prodromal phenomena	28	21	2	4
Bradycardia (rate below 80)	16	16	10	15
Angor animi	17	12	8	20
Pericardial friction rub	17	15	7	6
Pulsus alternans	10	9	6	14
Precordial hyperesthesia	8	8	3	8
Jaundice	6	6	5	10
Anuria	8	4	—	—
Hiccough	4	2	—	—
Uremia	3	2	—	—

ORIGINAL SITE OF PAIN (BEAN'S SERIES)

	NUMBER OF CASES
Substernal	88
Epigastric	29
Precordial	21
Left shoulder	5
Back	1

RADIATION OF PAIN (BEAN'S SERIES)

	NUMBER OF CASES
None	70
Left arm	23
Both arms	13
Both arms and both shoulders	8
Left arm and shoulder	8
Left arm and both shoulders	3
Right chest	3
Right arm	2
Left shoulder	2
Angle of scapula	2
Right shoulder	1
Left arm and jaw	1
Neck and jaw	1
Both arms and back	1
Back	1

TYPES OF PAIN (BEAN'S SERIES)

	NUMBER OF CASES
Crushing pressure	44
Squeezing, constricting, vicelike	29
Choking, smothering, suffocating	18
Sharp, stabbing, knifelike	11
Sore, aching, dull	11
"Excruciating"	7
Burning	5

Bean then lists fourteen categories of what he calls substitution symptoms which are reminiscent of the symptoms in some cases of our series:

SUBSTITUTION SYMPTOMS IN BEAN'S SERIES

SYMPTOMS	NUMBER OF CASES
Sudden onset of cardiac asthma, orthopnea, or pulmonary edema	11
Gradual increase in congestive failure	9
Sudden increase in severity of pre-existing failure	6
Weakness and syncope	4
Sudden onset of dyspnea and edema	4
Sudden onset of suffocation and choking	2
Sudden onset of palpitation, auricular fibrillation present	2
Vomiting, dizziness, and dyspnea	1
Angor animi and cardiac asthma	1
Dyspnea, weakness, and nervousness	1

SUBSTITUTION SYMPTOMS IN BEAN'S SERIES—(CONTINUED)

SYMPTOMS	NUMBER OF CASES
Dyspnea, weakness, and syncope	1
Severe weakness and increase in failure	1
Weakness and dizziness	1
Paralysis of left arm, paresthesia; no pain	1

The physical examinations in Bean's[128] series showed many more clinically demonstrable enlarged hearts than in our series, but the incidence of pre-existing hypertension in his series is not ascertainable, although it was probably much greater than in ours. Auricular fibrillation was also much more common in his series, occurring in thirty-five cases. A pericardial friction rub was heard in twenty-four cases of 176 (14 per cent), as against twenty-eight cases among our 400 survivors (7 per cent). As in our group of survivors, Bean found that the blood pressure remained elevated in a large number of cases, although the majority showed declining levels.

A pericardial friction rub was found in 10 per cent of Howard's[46] 165 cases, in 16 per cent of the 208 cases of Rosenbaum and Levine,[131] in 20 per cent of Levy's[141] fifty cases, and in only one of the 108 cases of Fisher and Zukerman.[137]

Electrocardiograms of the Survivors.—Electrocardiograms were taken in every case; in fact, no case was included in this study unless there was adequate electrocardiographic evidence to corroborate the clinical diagnosis of myocardial infarction. All of the original electrocardiograms were studied. In most instances the electrocardiograms were typical of recognized patterns associated with known myocardial involvement. The classical pattern representing anterior myocardial infarction was present in 176 instances (44 per cent), and the typical pattern of posterior infarction was noted in 113 instances (28 per cent). In fifty-six patients (14 per cent) the electrocardiogram was considered indicative of lateral, anteroposterior, posterolateral, or anterolateral infarction. Abnormal tracings without characteristic localizing features were present in fifty-five individuals (14 per cent), but in this group the electrocardiograms were considered as adequate to substantiate the clinical diagnosis of myocardial infarction. Thus, it is seen that there were more than one-half as many cases of posterior infarction as of anterior infarction among the survivors. This ratio may be compared with that shown subsequently of less than one-third as many cases of thrombosis of the right coronary artery as of the left anterior descending artery among the fatal cases, a difference which may serve to substantiate to some extent the statement sometimes made that occlusion of the right coronary artery is not so serious as occlusion of the left anterior descending artery.

Follow-up electrocardiograms* were taken during examinations made by the Veterans Administration, and in 353 of the original 400 patients these tracings

*Most of the electrocardiograms were made with the three standard leads and usually one or two precordial leads (CF_2 and CF_4 or CF_5).

were available for study. In addition, electrocardiograms from the other forty-seven patients, taken three to four months after the initial attack of myocardial infarction, were available. Electrocardiographic evidence of residuals of myocardial infarction was present in 366 (92 per cent) of the patients, while in thirty-four (9 per cent) instances the follow-up electrocardiogram was regarded as within the normal range. The break-down in the group of electrocardiograms which returned to normal was as follows: of 176 anterior infarctions, fourteen returned to normal; of 113 posterior infarctions, six returned to normal; of fifty-six lateral, anteroposterior, and posterolateral infarctions, four returned to normal; and in the fifty-five without localizing features, ten returned to normal.

Roentgenologic Evidence Among the Survivors.—Roentgenograms of the heart were taken in 394 of the 400 men during the first hospitalization for treatment of heart disease. In 314 instances (79 per cent of the entire group with roentgenographic examinations), the heart was considered to be of normal size and shape. In the remaining eighty patients the heart was considered enlarged, with seventy-eight instances of left ventricular enlargement and two of right and left ventricular enlargement. In four men pericardial effusion was diagnosed from the roentgenograms. Following fluoroscopy, pleuropericardial adhesions were suspected in three patients, and in five patients myocardial infarction of the left ventricle was suspected.

Pulmonary abnormalities were noted in the roentgenograms in twenty-one soldiers: bilateral pulmonary congestion was diagnosed in twelve patients, unilateral pulmonary infiltration in five, pulmonary infarction in three, and left pleural effusion in one patient. In all instances the pulmonary lesions cleared up.

From a roentgenographic point of view the aorta was considered abnormal in twenty-one subjects; in nine cases there was simple widening and in eleven, definite tortuosity. In only one patient was a calcified plaque demonstrated in the aorta.

Temperature, White Blood Cell Count, and Sedimentation Rate.—In the series of 400 survivors temperature records were available in 370 patients, leucocyte counts in 396, and sedimentation rates in 379, but all three of these studies were recorded in only 274 patients during the "acute attack" and, thereafter, sufficiently often to be valuable for correlation of all three factors.

In these 274 cases the temperature records were adequate for review. There were fifty afebrile patients. In seventy patients the highest temperature reached during the "attack" was between 99 and 99.9° F.; in 129 patients, between 100 and 101.9° F.; and in 25 patients the temperature reached 102° F. or more. When fever was present the temperature curve followed a definite pattern. The temperature started to rise in four to forty-eight hours following the onset of symptoms and reached the peak of elevation in another twenty-four to thirty-six hours. It returned to normal by lysis in another forty-eight to seventy-two hours. The temperature was normal by the ninth day after the onset of the attack in all but one instance in which the course was complicated by acute thrombophlebitis of the right leg.

The white blood cell count remained entirely within the normal range in fifty-five of the 274 soldiers throughout the period of hospitalization. There were thirty-eight patients with slightly increased white blood cell counts (9,000 to 10,000 per c. mm. of blood), 163 with moderately increased counts (11,000 to 19,000 per c. mm. of blood), and eighteen with high white blood cell counts (over 19,900 per c. mm. of blood). In 69 per cent of the patients the count reached its highest value wihin twenty-four hours of the onset of the attack and prior to the peak value of the sedimentation rate. In 15 per cent the highest leucocyte count was noted during the second day, and in the remaining 16 per cent the greatest white blood cell count appeared from the third to the eleventh day, the majority of these being on the third and fourth days. The majority of the counts (83 per cent) returned to the normal range within the first twelve days after the onset of the attack. In the remaining 17 per cent the count reached normal two weeks or more after the onset, and in more than two-thirds of these, before the end of the third week. In two patients the count remained slightly elevated throughout the period of hospitalization. The curves of rise and decline of the white blood cell count were similar whether the count was slightly elevated, moderately elevated, or high at the peak.

In fifty-eight of the 274 patients the sedimentation rate remained normal throughout the period of hospitalization; in twenty-three patients the rate became slightly increased (13 to 16 mm. per hour), in eighty-eight patients it became moderately increased (17 to 29 mm. per hour), and in 105 patients it became greatly increased (30 mm. or more per hour). The time interval between the onset of the attack and the day on which the sedimentation rate was greatest varied considerably and had no apparent relationship to the degree of leucocytosis and/or the height of the temperature elevation. In 72 per cent of the patients with increased sedimentation rates the greatest increase in rate occurred from the first to the ninth day after the onset of symptoms, with an almost even distribution for the days of this period. In 20 per cent of the patients with increased rates the greatest increase occurred between the tenth and fifteenth days after the onset of the attack. In the remaining 8 per cent the greatest increase in rate occurred at various intervals from the nineteenth to the fifty-second day.

The time interval between the onset of the attack and the return of the sedimentation rate to the normal range varied greatly and did not assume any characteristic pattern, although there was a tendency for the rate to return to normal between the fifteenth and the fortieth days after the onset (53 per cent). The return to normal occurred within the first two weeks in very few instances (7 per cent). In some patients (22 per cent) the return to normal occurred only after a prolonged period of hospitalization (as much as 119 days). In the remaining 18 per cent of the patients the sedimentation rate remained increased throughout the period of hospitalization.

In regard to the correlation between the degree of increase of the sedimentation rate and the time at which the greatest increase occurred and the time of return to normal, there was no significant difference among the three groups, although there was a slightly increased tendency for those patients with the

greatest increase in rate to have a longer period before return of the rate to normal.

A comparison was made of the three factors of temperature, white blood cell count, and sedimentation rate. The results are shown in Tables XXV, XXVI, and XXVII.

TABLE XXV. TEMPERATURE IN RELATION TO WHITE BLOOD CELL COUNT AND SEDIMENTATION RATE DURING ACUTE MYOCARDIAL INFARCTION OF SURVIVORS

	TEMPERATURE							
	AFEBRILE		99 TO 99.9°F.		100 TO 101.9°F.		102°F. OR MORE	
	NO.	%	NO.	%	NO.	%	NO.	%
White Blood Cell Count								
Normal	17	34	23	33	15	12	0	0
9,000 to 10,000	13	26	13	19	10	8	2	8
11,000 to 19,000	19	38	32	45	92	71	20	80
20,000 and over	1	2	2	3	12	9	3	12
Total	50	100	70	100	129	100	25	100
Sedimentation Rate								
Normal	16	32	22	31	17	13	3	12
13-16 mm./hr.	8	16	5	8	9	7	1	4
17-30 mm./hr.	18	36	21	30	45	35	4	16
31 mm./hr. and over	8	16	22	31	58	45	17	68
Total	50	100	70	100	129	100	25	100

TABLE XXVI. WHITE BLOOD CELL COUNT IN RELATION TO SEDIMENTATION RATE AND TEMPERATURE DURING ACUTE MYOCARDIAL INFARCTION OF SURVIVORS

	WHITE BLOOD CELL COUNT							
	NORMAL		9,000 TO 10,000		11,000 TO 19,000		20,000 AND OVER	
	NO.	%	NO.	%	NO.	%	NO.	%
Sedimentation Rate								
Normal	19	34	12	32	25	15	2	11
13-16 mm./hr.	3	6	7	18	11	7	2	11
17-30 mm./hr.	18	33	9	24	58	35	3	17
31 mm./hr. and over	15	27	10	26	69	43	11	61
Total	55	100	38	100	163	100	18	100
Temperature								
Afebrile	17	31	13	34	19	12	1	5
99-99.9°F.	23	42	13	34	32	20	2	11
100-101.9°F.	15	27	10	27	92	56	12	67
102°F. or more	0	0	2	5	20	12	3	17
Total	55	100	38	100	163	100	18	100

TABLE XXVII. SEDIMENTATION RATE IN RELATION TO WHITE BLOOD CELL COUNT AND TEMPERATURE DURING ACUTE MYOCARDIAL INFARCTION OF SURVIVORS

	SEDIMENTATION RATE							
	NORMAL		13 TO 16 MM./HR.		17 TO 30 MM./HR.		31 MM./HR. AND OVER	
	NO.	%	NO.	%	NO.	%	NO.	%
White Blood Cell Count								
Normal	19	33	3	13	18	20	15	14
9,000 to 10,000	12	21	7	30	9	10	10	10
11,000 to 19,000	25	43	11	48	58	66	69	66
20,000 and over	2	3	2	9	3	4	11	10
Total	58	100	23	100	88	100	105	100
Temperature								
Afebrile	16	27	8	35	18	20	8	8
99 to 99.9°F.	22	38	5	22	21	24	22	21
100 to 101.9°F.	17	30	9	39	45	51	58	55
102°F. or more	3	5	1	4	4	5	17	16
Total	58	100	23	100	88	100	105	100

The general picture, therefore, was one of elevated temperature, leucocytosis, and increased sedimentation rate. Of the 274 patients studied on the basis of these factors, there were 226 with increased temperatures, 220 with elevated white blood cell counts, and 216 with increased sedimentation rates, the incidence of these abnormal findings being approximately the same for each of the three factors. The correlation among the three factors was significant. They were jointly abnormal in 159 (58 per cent) of the patients; in seventy-six (28 per cent) of the patients two of the factors were abnormal; and in thirty-three (12 per cent) of the patients one of the factors was abnormal. There was no tendency noted for any one pair of factors to occur more often than any other pair, or for any one factor to occur singly more often than any other factor. There were only six (2 per cent) of the patients with normal values for all three factors. Thus, it appears that, typically, elevation of at least one of the three factors should occur during the course of acute myocardial infarction, and most often, that joint elevation of all three factors will be found. The following tabulation summarizes the interrelationship of the three factors in the 274 patients:

	SEDIMENTATION RATE		
NUMBER OF PATIENTS WITH:	NORMAL	INCREASED	TOTAL
Normal temperature and normal white blood cell count	6	11	17
Normal temperature and increased white blood cell count	10	21	31
Increased temperature and normal white blood cell count	12	25	37
Increased temperature and increased white blood cell count	30	159	189
Total	58	216	274

Other Laboratory Tests.—

Urinalysis: In all 400 cases of the survivors, at least one routine urinalysis was made during hospitalization. In sixty instances there were abnormal findings. Albuminuria was present in thirty patients, erythrocytes in twenty-four, casts in twenty (hyalin in seven, granular in nine, and both in four), and sugar in two. Albumin and red blood cells were found together in thirteen patients, albumin and granular casts in three, albumin and hyalin casts in three, and red blood cells and hyalin casts in one.

Blood Sugar Levels: In sixty-five patients blood sugar determinations were made during or within a few days of the acute attack. In all, the results were within normal limits. In seven of the sixty-five cases glucose tolerance tests were performed and all were normal.

Blood Nonprotein or Urea Nitrogen Estimation: These tests were performed in fifty-five patients and were entirely normal in fifty. In five patients the blood nonprotein nitrogen was elevated: 45, 46, 47, 8, 87, and 92 mg. per cent, respectively; all of these elevations occurred during the acute attack. In all five patients the levels returned to normal during the period of initial hospitalization.

Blood Cholesterol Determinations: In sixty-six patients the blood cholesterol level was determined during or shortly after the acute attack. A range of 150 to 250 mg. per cent being considered normal, the levels were normal in forty-three instances and elevated in twenty-three. In eight patients the levels were between 265 and 300; in nine, between 299 and 350; in three, between 349 and 400; in one, at 400; in one, at 450; and in one, at 505 mg. per cent.

CLINICAL COURSE OF THE SURVIVORS

General Features.—All of the men who survived an attack of acute myocardial infarction were observed and treated in an Army Hospital before discharge from service. Two hundred twenty-nine patients (57 per cent of the entire group) had an uneventful convalescence and were entirely asymptomatic after recovery from the "acute attack." The most common symptom was recurrent pain, usually substernal, precordial, or limited to the left side of the chest. These attacks of pain occurred in ninety-eight, 25 per cent of the patients; but in only nine instances could these attacks of pain be considered of major importance and probably representative of the occurrence of a fresh attack. In the majority of patients the pain was of anginal type and associated with increased activity after the patient became ambulatory. In twenty-seven patients (7 per cent) the clinical course during the Army hospitalization could be considered as "stormy," inasmuch as the patients were critically ill and the outcome uncertain for days and weeks. Myocardial insufficiency was considered to be present in twenty-two men, in six of whom there was frank cardiac decompensation with edema of the lower extremities, enlarged liver, or other abnormalities. In sixteen men of the group with myocardial insufficiency, pulmonary congestion was the complicating clinical feature, and in three of these patients, pleural effusions were present. All patients with congestive heart failure recovered from the cardiac decompensation.

Transient pericarditis was noted in twenty-eight instances; in one of these, pericardial effusion developed.

In the order of their frequency the clinical features of the "acute attack" during hospitalization were as follows:

Recurrent pain	98
Pericarditis	28
"Stormy course"	27
Heart failure	22
Pulmonary congestion only	16
Frank failure	6
Dyspnea without râles	19
Vomiting (not associated with drugs)	12
Sweating	11
Weakness and tiredness	10
Confused, psychotic, disoriented state	6
Numbness of extremities	6
Palpitation	6
Restlessness (marked)	6
Pulmonary infarction	5
Pneumonia (with both clinical and x-ray evidence)	5
Smothering sensation	4
Dizziness	3
Pleural effusion	3
Unconsciousness	3
Abdominal distension	2
Orthopnea	2
Nausea	1
Paresis of arms (transient)	1
Blanching of left leg	1

In twelve instances other specific disease states were found to have existed or developed during hospitalization, as follows:

Exfoliative dermatitis	1
Mumps	1
Polycystic kidney disease	1
Carotid sinus syndrome	1
Fröhlich's syndrome	1
Gout	1
Thrombophlebitis	1
Infectious mononucleosis	1
Diabetes mellitus	1
Hypothyroidism	1
Hydronephrosis with double ureter	1
Acute respiratory infection	1

First Clinical Diagnosis in the Patients Who Survived.—An analysis was made of the first clinical impression or diagnosis given in the 400 patients who were finally diagnosed as having coronary thrombosis or myocardial infarction. In 283 patients (71 per cent) the initial clinical impression was in agreement with the final diagnosis. In eighty-one patients (20 per cent) coronary arteriosclerotic

heart disease was not regarded as a clinical possibility and an entirely different diagnosis was made. A study of these various diagnoses reveals a long list of the conditions that should be considered in the differential diagnosis of coronary thrombosis or myocardial infarction. In thirty-six patients (9 per cent) no diagnosis was offered at the time of the first recorded clinical examination; in these patients coronary artery disease was apparently never considered as a clinical possibility.

In many records lengthy discussions as to the diagnostic possibilities were made by the ward surgeons, and from these data two definite trends were noted. In many instances the clinical picture was so obviously the classical one of acute coronary thrombosis with myocardial infarction that in spite of the relatively early age of the patient no other diagnosis was even suggested. On the other hand, many examiners felt that although the clinical picture resembled that of coronary thrombosis, such a diagnosis was precluded by the relative youth of the patient.

Diagnoses considered previous to arrival at the final diagnosis of acute coronary artery occlusion and myocardial infarction are listed as follows:

PRIMARY DIAGNOSES OTHER THAN CORONARY ARTERY DISEASE

Pleurisy	10
Gastritis	10
Psychoneurosis	9
Essential hypertension	5
Peptic ulcer	5
No heart disease	4
Rheumatic heart disease	4
Pericarditis, acute	4
Neurocirculatory asthenia	3
Nasopharyngitis	3
Diaphragmatic hernia	3
Pneumonia	3
Heat exhaustion	2
Functional heart disease	2
Cardiac arrhythmia	2
Bronchitis, acute and chronic	2
Volvulus	1
Spontaneous pneumothorax	1
Cholelithiasis	1
Dissecting aneurysm	1
Bronchial asthma	1
Malaria	1
Myalgia, pectoral	1
Cardiospasm	1
Intercostal neuralgia	1
Pulmonary pathology	1

SECONDARY DIAGNOSES OTHER THAN CORONARY ARTERY DISEASE

Psychoneurosis	2
Cardiac arrhythmia (noncoronary)	2
Intercostal neuralgia	2
Pleurisy	2
Sliding acquired hernia	1
Hiatus hernia	1
High intestinal obstruction	1
Acute cholecystitis	1
Cholelithiasis	1
Acute gastritis	1
Acute gastric ulcer	1
Esophageal pathology	1
Pneumonia	1
Lung cyst	1
Pulmonary edema	1
Bronchitis, acute	1
Pericarditis	1
Essential hypertension	1
Endocarditis (possible)	1
Cerebral angiospasm	1
Herpes	1
Left perinephritic abscess	1
Congenital heart disease	1

SUBSEQUENT COURSE OF THE SURVIVORS

All of the 400 survivors have come under the jurisdiction of the Veterans Administration for purposes of treatment and pension. They have been examined by cardiologists in the various outpatient departments and/or hospitals of the Veterans Administration. Detailed histories, physical examinations, and laboratory investigations have been made, and in 334 cases complete records were available; in the remainder some data were also available.

The 400 men were treated in Army hospitals for six weeks to eight months and were discharged from the service only after the apparent maximal benefit of hospitalization had been attained, every one being ambulatory. Subsequently two patients have been followed for less than one year, 154 for twelve to twenty-three months, 175 for twenty-four to thirty-five months, fifty-six for thirty-six to forty-seven months, and thirteen for more than forty-eight months.

Since discharge from the Army, forty-eight veterans have had to be hospitalized for treatment of the cardiac condition; seventeen have experienced and survived another acute attack of myocardial infarction, and twenty-eight have been treated for definite congestive failure.

The most prominent symptom after discharge from the Army has been dyspnea on exertion. This symptom was present in 208 (62 per cent) of the 334 patients for whom detailed records were available. Twenty of these men have experienced attacks of orthopnea and six have had attacks of nocturnal dyspnea, but only ten have had dyspnea continuously at rest.

The next most prominent symptom has been angina of effort, which was present in 175 (52 per cent) of the 334 cases. Two hundred twenty-seven men

gave no history of angina of effort before the attack, and 137 of this group have had these symptoms since the attack. Data were available in fifty-seven of the seventy-three patients with angina of effort before the attack; in thirty-eight of these the angina has persisted, while in nineteen there has been no angina since the attack.

In thirty-one additional patients in whom there was no angina of effort before the attack there have since been episodes of thoracic pain which were usually of short duration and in no way associated with exertion. In four other patients there has been a vague history of thoracic pain not associated with exertion; this symptom occurred in patients who had had the anginal symptoms prior to the attack.

A prominent symptom experienced by sixty-five of the 334 men has been a feeling of tiredness, described by such phrases as "easily fatigued," "no pep," "tired out with exertion," and "tired feeling all the time." Weakness was present in twenty-seven patients. Palpitation was noted in forty-two patients and was described by the phrases, "can feel the heart beat" (fifteen patients), "heart palpitates" (twelve patients), "heart jumps" (ten patients), and "heart pounds" (five patients). A number of patients (thirty) have become extremely nervous, apprehensive, and frightened since the attack. Nervous symptoms were reported as dizziness (twenty-five patients), headache (fifteen patients), fainting spells (eleven patients), insomnia (five patients), and hemiplegia (one patient).

Other symptoms noted since the attack have been cough (nine patients), choking attacks (six patients), tingling and numbness of the arms and hands (six patients), smothering attacks (four patients), tingling and numbness of the arms and legs (three patients), and indigestion (three patients).

Reports of physical examinations since discharge from the Army have been available in 342 cases, in 221 of which they were regarded as normal and in the other 121 as abnormal. Enlargement of the heart was noted in forty-eight of the latter, and this observation was verified by roentgenographic examination. Heart sounds were described as faint, distant, of poor quality, or barely audible in fifty-three patients. There were clinical signs of congestive failure in twenty-eight patients, in twelve of whom there was pitting edema of the feet and ankles; in five there was pulmonary congestion, and in eleven, the signs of more advanced congestive failure such as pulmonary râles, enlarged, tender liver, and edema of the lower extremities. In twenty-two patients systolic murmurs were detected, in twenty over the mitral area, in one over the aortic area, and in one along the left border of the sternum. In no instance was the murmur considered representative of an organic valvular lesion. Cyanosis was described in twenty-one patients. Premature contractions were noted in eighteen patients; sinus tachycardia with a rate over 100 per minute was recorded in twenty-one; gallop rhythm was heard in five; and pulsus alternans was detected in two patients.

In summary, in 248 cases the condition of the men has been regarded as stationary, in ninety-four as improved, in twelve as one of early improvement followed by relapse, and in forty-six as progressive, with increase in degree of impairment.

A statement as to the industrial history of 361 veterans since discharge from the Army is available. Of this group, 181 (50 per cent) have returned to full-time employment, and eighteen (5 per cent) are employed part-time. Twenty men (5 per cent) attempted to work but had to stop because of their physical condition, and 127 (36 per cent) have not been employed at any time. Fifteen veterans (4 per cent) have been attending school under the vocational rehabilitation training program of the Veterans Administration.

NEGRO PATIENTS

Because of the apparent dearth of information concerning coronary artery disease in Negroes, it was considered advisable to give the data separately for these patients. In our series there was a total of sixty-three Negroes, of whom twenty-six died and thirty-seven survived. The fatality rate among the Negroes was 41 per cent as compared with a rate of 55 per cent for the 803 white men.

Fatal Cases of Negroes.—Twenty-six Negroes under 40 years of age died of coronary artery disease during service in the Army. The age distribution of this group is as follows:

AGE IN YEARS	NUMBER OF CASES
21	1
23	1
26	2
28	1
29	1
30	2
31	2
32	4
33	2
34	3
35	2
36	1
38	2
39	2

The average age of this group at the time of the "attack" was 31.9 years, as compared with 32.4 years for the group of Negroes who survived the attack of coronary artery disease during military service.

Only six of the twenty-six men gave a past history of previous symptoms attributable to heart disease. The past clinical features in these six cases were as follows: one patient had had an attack three months before the final attack, one had experienced dyspnea on severe exertion, one had noted epigastric distress at times, one had had attacks of palpitation with precordial pain during the preceding six months, one had had a spell of syncope two months before the actual attack, and a sixth had experienced pains in the legs one month before the actual "coronary attack."

The most striking clinical feature of this group of Negroes who died in the Army was the large number who did not experience pain as a symptom of the "coronary attack." Only fourteen men (54 per cent) gave a history of pain,

whereas in twelve patients there is no record of any pain (in one of these the existence of pain would be better listed as "unknown"). On the other hand, among the group of Negroes who survived the attack thirty-four (92 per cent) of the thirty-seven men experienced pain as the outstanding clinical feature.

Among the fourteen men who experienced pain, this pain was localized over the precordium in seven instances, in the sternal region in two, in the epigastrium in two, in the upper back and epigastrium in one, in the right lower quadrant in one, and in the anterior chest region in one. Radiation of the pain was an uncommon clinical feature and occurred in only two instances, once from the sternum to the left arm and in another patient, from the epigastrium to the upper back.

Among the Negroes who survived the coronary attack, radiation of the pain was not a very common clinical feature, occurring in ten of thirty-four patients who had pain.

Other symptoms which accompanied the acute attack among the Negroes who died during Army service were dyspnea, nausea and vomiting, and congestive heart failure, to mention the most common. Dyspnea was present in four patients, vomiting alone in four, nausea and vomiting in two, nausea alone in one, and congestive heart failure in three patients. Other findings occurring only once each were rapid pulse, gasping, weakness, pallor, constipation, "gas," convulsions, and unconsciousness.

Among the men who survived there was a much higher percentage with a past history of probable heart disease, and a considerable number of them had experienced rather typical anginal symptoms before the onset of the actual attack, whereas in the group of patients who died there was only one man with a possible anginoid history. Over 90 per cent of the men who survived experienced pain during the "acute attack," whereas only 53 per cent of those who died are known to have had pain. However, some of the men who died suddenly may not have been questioned or were too ill to give a history.

The duration of illness in the twenty-six men who died was as follows: three had a sudden collapse, eight survived from a few minutes to one-half hour after the onset of the attack, six lived from one-half to four hours, three lived from four to twelve hours, and six lived longer than twenty-four hours: ten days, fourteen days, thirty-six days, seven months, eight months, and eight months, respectively.

Pathology.—For the twenty-six Negroes who died, the pathologic data related to the heart may be summarized as follows: Simple narrowing of the coronary arteries was present in six patients, and in one of these there was an infarct in the left ventricle. Sclerotic occlusion of a main coronary artery was present in five patients; the right coronary artery was involved in one instance, and the left anterior descending coronary artery was involved in four. Fresh thrombotic occlusion was present in ten cases. These thrombi involved the left anterior descending artery in eight patients, one of whom showed an organizing infarct in the anterior wall of the heart; another, an infarct in the left auricle with practically complete sclerotic occlusion of all the larger arteries, and a third, practically

complete sclerotic occlusion of all main arteries. In two patients the fresh thrombotic occlusion involved the right coronary artery.

Thrombosis featured two other cases. In one patient the lesion was described as a thrombus in the right coronary artery with a large infarct of the left ventricle, and in the other, as an organizing thrombus of the left anterior descending coronary artery.

In addition, there were two patients in whom there was an old thrombus in the left anterior descending artery with an old anterior infarct, and one with an old thrombus in the right coronary artery.

Surviving Negroes.—The age distribution of the thirty-seven Negroes who survived was as follows:

AGE IN YEARS	NUMBER OF CASES
20	1
21	1
27	2
28	3
30	4
31	3
32	3
33	4
34	2
35	3
36	4
37	3
38	4

Average age: 32.4 years

The height-weight relationship of the Negro group was similar to the entire group. Fifteen subjects (41 per cent) were below the normal standard, four being much below normal and eleven, moderately below normal. Eight subjects (26 per cent) were in the normal range, while fourteen (38 per cent) were above the normal range. Nine of these latter men were moderately above normal and five were much above normal.

The history relative to the previous existence of heart disease revealed the same trend as among the entire 400 survivors. Seventeen had no previous history of heart disease. Sixteen (43 per cent) presented histories of some cardiovascular disorder; ten had histories rather typical of the anginal syndrome, three were known to have had a previously existing hypertension, and three had had a previous diagnosis of definite organic heart disease. Four other patients gave a history that was suggestive of heart disease.

Only seven Negroes gave a history of some cardiovascular disturbance in the immediate family; the other thirty men in the group had no knowledge of any family history of heart disease. The family history of the seven men in whom it was significant could be listed as follows: one brother with "heart disease"; two mothers living with high blood pressure; two fathers dead of cardiac decompensation; one mother dead of "heart disease"; and one mother living with "heart disease." Thus, the incidence of known heart disease was much lower

among the Negro patients than among the white patients in this series. Among the surviving Negroes a knowledge of heart disease in the immediate family was admitted by only seven (11 per cent), whereas among the surviving white patients, 163 of 363 (43 per cent) gave a definite history of heart disease in the immediate family. This difference in family history between the two groups may be due to the difficulties in obtaining accurate histories from the Negro patients.

All of the Negroes included in this study presented clinical evidence, supported by electrocardiographic data and other laboratory findings, to support the final Army diagnosis of myocardial infarction. In twenty-one the onset was sudden and dramatic; in six a typical anginal syndrome had existed for at least six weeks preceding the attack of myocardial infarction; in five there was a history of long-standing, somewhat vague symptoms; and in five, symptoms suggestive of a "prodromal" attack occurred five to fifteen days before the acute episode.

As with the entire group of men included in this study, pain was the outstanding clinical symptom. Thirty-four of the thirty-seven Negro survivors experienced pain as the primary and most important symptom accompanying the onset of the attack of myocardial infarction. The pain was located as substernal in eleven cases, precordial in eight, left chest in six, epigastric in five, and in the chest without more definite localization in four.

The pain was localized in twenty-four instances and radiated to various parts of the body in ten others. The pain radiated to the left shoulder in three patients, to the left arm in two, to the substernal area in two, to the left axilla in one, between the shoulders in one, and to the left scapula and upward into the neck in one.

The initial pain was aggravated by respiration in four patients (10.8 per cent); this corresponds closely with the thirty-seven instances of this clinical finding among 363 white patients.

In the three patients without pain, the initial symptoms were palpitation caused by runs of premature ventricular contractions in one and dizziness in two. In all three the onset of the attack was also accompanied by dyspnea.

Other symptoms that were present during the "acute attack" and followed the initial symptoms were: dyspnea in eighteen patients, weakness in seven, sweating in five, vomiting in three, loss of consciousness in three, palpitation in two, and dizziness in two; semiconsciousness, anorexia, diarrhea, headache, warm feeling over the body, smothering sensation, and numbness of the extremities were each described once.

Blood pressure readings were obtained in the majority of patients at the time of induction into the Army and during the "acute attack." In only one patient was the blood pressure reading not recorded during the "acute attack" or at the time of induction, and in one other patient the record during the "acute attack" was not available. In the remaining thirty-five patients the induction blood pressures were normal in twenty-eight, slightly elevated in three, and not recorded in four. During the "acute attack" the first blood pressure taken during the initial physical examination was normal in eighteen, slightly elevated

in seven, moderately elevated (150/120) in one, low in five, and not taken in four patients.

In the seven patients in whom the blood pressure was slightly elevated during the "acute attack" the induction blood pressures were normal in five and slightly elevated in one, and in one the induction blood pressure was not recorded. In the one patient in whom the blood pressure was moderately elevated during the "acute attack" the induction blood pressure was normal.

A review of the records of the physical examinations revealed findings similar to those in the entire series. In nineteen patients, the physical examinations were entirely within normal limits. Arrhythmias were the most common deviation from the normal. There were four patients with premature ventricular contractions, four with sinus bradycardia (rates between 50 to 60), one with transient auricular fibrillation, and one with sinus tachycardia.

The heart sounds were described as faint or of poor quality in three patients; gallop rhythm was present in two; transient, nontransmitted apical systolic murmurs were present in three; and an accentuated, tambourlike aortic second sound was heard in one patient. Pericardial friction rubs were heard in two patients at the initial examination and in another case on the third hospital day. Pulmonary edema was considered to be present in three individuals. Frank, clinical shock with pallor, cyanosis, and sweating was present in one patient. The only sign of aging noted on the physical examinations was arcus senilis in two patients.

The diagnosis of arteriosclerotic heart disease as coronary occlusion, thrombosis, or myocardial infarction was made initially in twenty-one (57 per cent). Among the white patients the first clinical impression was listed as coronary arteriosclerotic heart disease in 283 (71 per cent). In thirteen patients the first diagnoses differed from the final clinical diagnosis of myocardial infarction. In three patients the diagnosis was deferred without any recorded evidence that possible coronary artery disease actually existed.

The following is a list of the first clinical impressions which were later considered incorrect: essential hypertension was recorded in two patients; and functional heart disease, psychoneurosis, pleurisy, intercostal neuralgia, chronic bronchitis, penetrating duodenal ulcer, perforated peptic ulcer, hiatus hernia, "eventration of the stomach into the lungs," gastric ulcer, and gastroenteritis were each recorded in one patient.

Electrocardiograms were available in all of the thirty-nine Negro patients. In thirty-two the records revealed classical localizing features of myocardial infarction. In fifteen the records were characteristic of anterior infarction, in fourteen, of posterior infarction, in two, of posterolateral involvement, and in one, of lateral infarction. In five patients there was not sufficient evidence to localize the lesion definitely, and in these the electrocardiograms were interpreted as representing myocardial damage.

From the data concerning the sixty-three Negroes in one series it is obvious that we cannot agree with Hunter[97] that the symptomatology of coronary artery occlusion in Negroes is different from that in Caucasians, at least in men under 40 years of age. None of Hunter's sixteen Negro patients had pain, whereas

all had congestive failure of long standing, and the acute coronary artery occlusion was heralded by an exacerbation of the symptoms of the congestive failure. It is evident that Hunter was dealing with an entirely different category of patients, and undoubtedly an older group. Apparently Negroes with acute coronary artery occlusion are rarely hospitalized in civil life, if one is to judge from the literature.

SIXTEEN ADDITIONAL CASES IN WHICH DEATH OCCURRED

In addition to the 850 cases thus far described there were sixteen in which death occurred but which were not adequately examined by us from the standpoint of the pathologic anatomy. The clinical records of these cases were adequate and were thoroughly reviewed. All of the patients were discharged from the Army because of myocardial infarction. A summary of the clinical features of these sixteen cases follows:

AGE IN YEARS	NUMBER OF CASES
23	1
30	1
33	1
34	1
35	2
36	1
37	3
38	2
39	4

Nothing was apparent in the clinical course or follow-up studies that was remarkably different from the same features in the 400 cases of nonfatal myocardial infarction.

Twelve of the sixteen patients gave no previous history of any cardiovascular disease, two had experienced definite anginoid attacks for three to six months previous to the actual acute episode, and two were known to have had a relatively severe arterial hypertension for several years.

The clinical picture of the acute attack of myocardial infarction was sufficiently typical to lead the clinicians to diagnose the nature of the disease correctly in fourteen of the sixteen patients. In the other two patients the diagnoses were congestive heart failure of undetermined cause and possible rheumatic heart disease.

The onset of the "acute attack" of myocardial infarction was sudden and without any previous warning in twelve cases; in three patients the onset was gradual over periods of one to six months, and in two of these three cases the men previously had had rather typical attacks of angina of effort. One patient did not experience definite pain at any time during the clinical course, and the symptoms started with weakness and shortness of breath followed by frank congestive heart failure.

Pain was the outstanding clinical symptom and was present in fifteen of the sixteen patients, being the primary symptom in eleven, whereas in two patients the primary symptom was a feeling of tiredness, and in one it was sudden marked

dyspnea. The pain was classical in all instances. The initial pain radiated in eleven instances; the distribution of this radiation was to both arms in five, to left shoulder and arms in three, and to left chest, neck, and right arm, and to left arm and neck in one patient each. In four patients there was no radiation of the pain.

Reports of complete physical examinations made during the initial attack were available in all sixteen cases. The cardiac examination in nine patients was reported as entirely normal; transient systolic apical murmurs were heard in three, and transient gallop rhythm and premature ventricular contractions were each noted in two patients. Tachycardia of moderate degree was noted in three patients, and bradycardia was observed in one.

Pulmonary congestion was detected in three patients, in one of whom there was congestive heart failure. One patient was in severe shock with the accompanying pallor, cyanosis, and cold, clammy skin.

Roentgenograms of the chest were available for all patients of this group. In eleven patients the heart was considered to be of normal size and shape. In five patients the heart was reported to be enlarged, in three of whom the enlargement was reported as marked, and in one patient a large ventricular aneurysm was later noted during the period of hospitalization.

Electrocardiograms revealed classical changes of acute myocardial infarction in all but one patient. The electrocardiographic pattern was classical for anterior infarction in seven patients, typical of posterior infarction in six, diagnostic of posterolateral infarction in one and of anteroposterior infarction in one, and indicative of myocardial damage in one.

Analysis of the blood pressures made during the acute attack of myocardial infarction showed a drop below normal standards in two patients; in six the pressures remained within normal range, in four the pressures were definitely elevated, and in four no blood pressure records were available. The induction blood pressures were normal in nine patients, definitely elevated in four, and not recorded in two. All of the elevated blood pressure readings noted during the acute attack occurred in men with normal induction blood pressure readings. In the four patients with elevated blood pressures at the time of induction the blood pressures were in the normal range in two during the acute attack, and in the other two, pressures were not recorded during the acute attack.

Temperature readings were available in twelve patients during the acute attack, and in all but one there was a definite elevation of temperature. The highest levels reached were 99 to 99.1° F. in four patients, 100 to 100.9° F. in one, 101 to 101.9° F. in two, and 102° F. or higher in four. In every case the temperature dropped to within normal limits no later than nine days after the onset of the acute attack.

Other available clinical data include sedimentation rates and white blood counts in fourteen of the cases. The sedimentation rate was normal in three patients, slightly elevated in one, moderately elevated in five, and markedly elevated in six. The leucocyte count was normal in two patients, slightly increased in two, moderately increased in nine, and greatly increased in one.

The clinical course in these sixteen cases was described as uneventful in seven patients, and as "stormy" and/or as having additional complications in nine. Congestive heart failure necessitated prolonged hospitalization for two patients; pulmonary infarction occurred in two, probable recurrent myocardial infarct in one, and frequent recurrent episodes of substernal pain with the slightest activity in two.

All of the patients were discharged as ambulant from the Army hospitals into civilian life. Because of their physical condition, none of these patients tried to gain employment. From the time of the first symptoms attributed to an acute attack of myocardial infarction the duration of life of patients in this group ranged from one and one-half months to thirty-two months. Four lived one and one-half to six months after the initial attack, seven lived between six and twelve months, two between one and two years, and three between twenty-four and thirty-two months. Seven patients died at home; there are no records available for four of these patients, and three members of this small group died suddenly and unexpectedly. There was no post-mortem information available for these seven patients. The remaining nine patients were hospitalized subsequent to their discharge from the Army hospital, eight in Veterans Administration hospitals and one in a private hospital. Recurrent myocardial infarction was responsible for the death of four of these patients and chronic congestive heart failure, in addition to the myocardial infarction, caused the death of three. Chronic congestive heart failure was responsible for two other deaths. Multiple pulmonary infarction was considered the cause of the death of another patient. One patient died suddenly with acute pulmonary edema after an acute illness of only ten hours. Another patient died shortly after the onset of hemiplegia and unconsciousness that were attributed to cerebral embolization. There were five autopsies performed in this group of patients, all confirming the diagnosis of previous myocardial infarction.

ILLUSTRATIVE CASES AMONG THE SURVIVORS

CASE 190 (Typical Anterior Myocardial Infarction).—A 28-year-old infantryman, whose former occupation was that of a painter, was inducted into the Army Jan. 20, 1943. His blood pressure then was 118/80, his height, 64.5 inches, and his weight, 141 pounds. His family history was irrelevant except possibly for the fact that his mother had bronchial asthma. The patient had used alcohol and tobacco moderately. In 1938 he had had an attack of pain in his precordium radiating down his left arm. On June 14, 1944, after climbing a steep hill, he had an attack of severe pain in the left thoracic region anteriorly, radiating down the left arm, which became numb. He vomited, became very short of breath, and was apprehensive. He entered the hospital the same day.

On admission he had an anxious expression, was writhing in pain, and was clutching his left chest. He was coughing and dyspneic and cyanotic. His heart was normal on examination. His pulse rate was 110 per minute and his blood pressure, 140/95. Later the same day the blood pressure was 144/108, and the following day it was 105/70, after which it remained at a normal level. The temperature rose from 97 to 101°F. and returned to normal by lysis after five days. The dyspnea and cyanosis gradually improved after the administration of oxygen, morphine, and bed rest. He was then asymptomatic after recovering from the acute phase of the "attack."

The white blood cell count was 17,700 with 78 per cent polymorphonuclear leucocytes on June 15; 11,500 with 86 per cent on June 20; and 8,950 with 48 per cent on June 26. Sedimentation rates were 8 mm. in one hour on June 20, 23 mm. on June 26, 10 mm. on July 1, 9 mm. on July 1,

9 mm. on July 29, and normal thereafter. The electrocardiograms went through the progressive changes of acute anterior myocardial infarction during the first thirteen weeks, as shown in Fig. 1. Roentgenograms of the chest made on June 25 and September 11 were normal.

The soldier was discharged from the Army on Nov. 1, 1944, with the diagnosis of arteriosclerotic heart disease and thrombosis of the anterior descending coronary artery. He resumed his work as a painter.

Nine months after discharge the veteran was examined by physicians of the Veterans Administration. In the interval he had had symptoms of shortness of breath and precordial pain on exertion, with edema of the feet and ankles. Physical examination revealed the heart to be of normal size and a faint systolic murmur at the mitral area. The heart sounds were of normal quality, except that the aortic second sound was accentuated. The diagnosis was coronary artery sclerosis with the anginal syndrome.

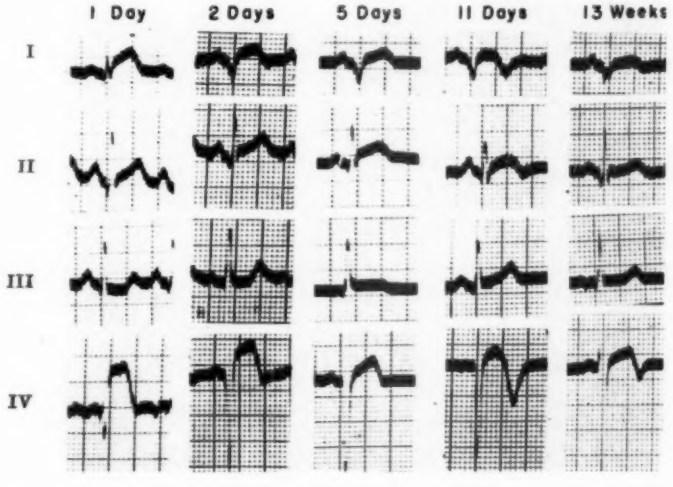

Fig. 1.—Case 190. Survivor, 28 years of age. Typical anterior myocardial infarction.

CASE 92 (Typical Posterior Myocardial Infarction).—A 25-year-old white infantry staff sergeant, whose former occupation was that of a laborer in a brass foundry, was inducted into the Army Oct. 12, 1941. At that time his blood pressure was "normal," his height, 67 inches, and his weight, 170 pounds. His family history was irrelevant, and his past history was negative for cardiovascular disease. He smoked moderately and denied the use of alcohol.

On April 3, 1943, while checking supplies, the sergeant suddenly experienced a squeezing, viselike, retrosternal pain which radiated to both shoulders and down the arms to the fingers. He began to sweat and to have hot and cold sensations; he could neither get into a comfortable position nor catch his breath. He went to the dispensary and was relieved in five minutes by a hypodermic injection, but after forty-five minutes the symptoms returned. About six hours after the onset of symptoms the patient was hospitalized.

On admission the soldier appeared to be acutely ill, was restless, cold, clammy, perspiring, and of ashen color. The right pupil was larger than the left. He was very dyspneic and complained of a severe, viselike pain in the sternal region. The heart sounds were of poor quality. The rhythm was irregular because of premature contractions. The blood pressure was 120/80, the plus rate was 50, and the temperature, 99.6° Fahrenheit. The clinical diagnosis was coronary artery disease.

The blood pressure was normal throughout the entire period of hospitalization. The temperature rapidly became elevated; on the second day it was 99.4° F., on the third day, 101° F.,

on the fifth day, 99.2° F., on the sixth day, 99° F., and the seventh day and thereafter, normal. During the first forty-eight hours morphine, oxygen, and absolute bed rest were prescribed. After the acute phase, the clinical course was asymptomatic.

The white blood cell counts were 10,600 with 75 per cent polymorphonuclear leucocytes on April 4, 9,600 with 82 per cent on April 5, and 5,900 on April 16. The sedimentation rate was 3 mm. in one hour on April 5, 16 mm. on April 18, 5 mm. on April 20, and 1 mm. on April 28. Electrocardiograms showed the progressive changes of acute posterior myocardial infarction, as shown in Fig. 2. A roentgenogram of the chest was normal.

The patient was discharged July 23, 1943, with the diagnosis of acute coronary artery occlusion. He was examined seven months, and again two years and four months, after discharge from the Army. He complained of shortness of breath and a "catching" sensation across the upper part of the chest. No abnormal physical signs were elicited. The blood pressure was 116/80 and the heart rate, 80 per minute. A roentgenogram of the chest showed the heart and aorta to be normal. The diagnosis was coronary arteriosclerotic heart disease with previous coronary artery thrombosis, posterior myocardial infarction, and myocardial insufficiency.

Since discharge the patient has been gainfully employed at moderately hard unskilled labor.

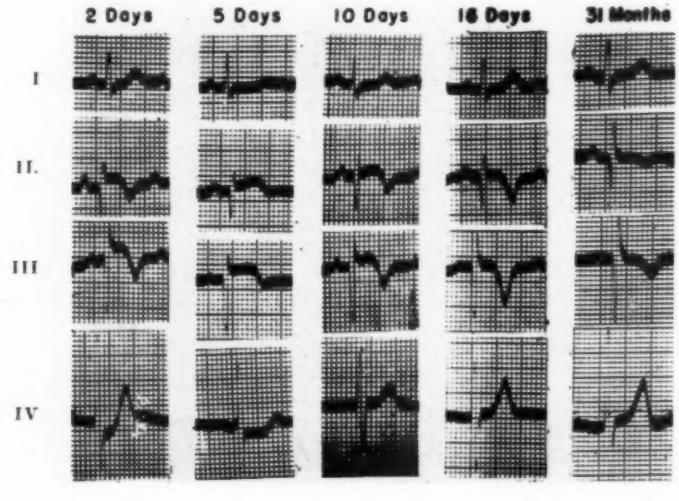

Fig. 2.—Case 92. Survivor, 25 years of age. Typical posterior myocardial infarction.

CASE 71 (Posterior Myocardial Infarction With Minimal Symptoms).– A 35-year-old white private, who before induction had been operator of a rubber mixing machine, entered the service March 3, 1943. His blood pressure at that time was 144/90, his height, 65 inches, and his weight, 232 pounds. His father had died at the age of 62 of a "heart attack." The patient had had mild hypertension for at least two years before his attack. He used tobacco moderately and alcohol occasionally. He had been obese for years. Prior to admission he had always felt well. While lifting some boxes on June 3, 1943, he suddenly developed a mild substernal ache which lasted for about two minutes and was associated with a tingling sensation down both arms. After this, he felt perfectly well, but because this had been the first instance of a physical complaint since he entered the Army, he reported to the medical officer. The latter, knowing the soldier's record, hospitalized him at once.

His complexion was florid and he appeared well; he weighed 220 pounds. His blood pressure was 160/100, his pulse rate was 84 per minute, and his temperature, 98° Fahrenheit. The physical examination was negative. The clinical impression, however, was coronary thrombosis and essential hypertension.

The course was entirely asymptomatic, but the temperature reached 101° F. in forty-eight hours and returned to normal by lysis by the eighth hospital day. Moderate leucocytosis and increased sedimentation rates returned gradually to normal. The blood pressure on the second day was 150/120 and thereafter attained normal levels, with an occasional slight systolic or diastolic elevation. The white blood cell count was 14,800 with 81 per cent polymorphonuclear leucocytes on January 4, 11,050 with 74 per cent on January 8, and 8,200 with 72 per cent on January 11. The sedimentation rate was 19 mm. in one hour on January 4, 58 mm. on January 8, 15 mm. on January 15, 8 mm. on February 6, and 5 mm. on February 12. A series of electrocardiograms showed typical evidence of posterior myocardial infarction, as shown in Fig. 3. A roentgenogram showed some prominence of the left ventricle, the transverse diameter of the heart being 15.8 cm., with the transverse diameter of the thorax 33.5 centimeters. The soldier was discharged from the Army on March 16, 1945. The final diagnosis was posterior myocardial infarction, probably due to coronary artery sclerosis with occlusion.

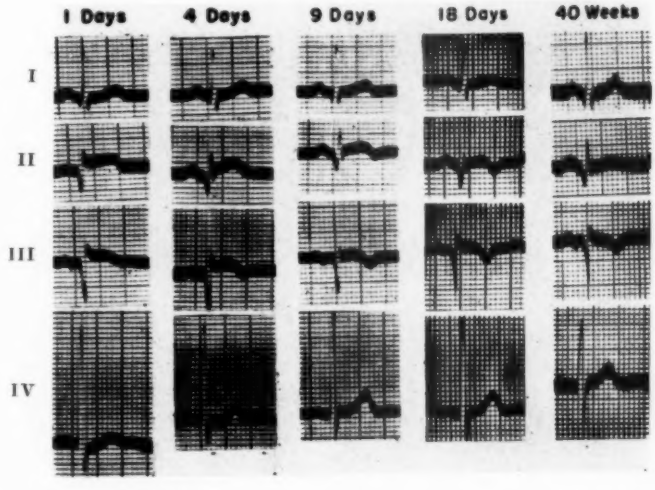

Fig. 3.—Case 71. Survivor, 35 years of age. Posterior myocardial infarction with minimal symptoms.

The veteran was examined on Sept. 13, 1945, six months after discharge from the Army. He had no complaints. His weight was 238 pounds. The blood pressure was 146/104 and the pulse rate, 96 per minute. The physical examination was negative. Roentgenogram of the chest showed the left border of the heart to be rounded, with a transverse diameter of 16.5 centimeters. The man had been working full time at the same job he had formerly held.

CASE 327 (Prodromal Symptoms for Three Weeks).—A 30-year-old white staff sergeant, whose former occupation had been that of bus driver, had been inducted into the Army Oct. 7, 1941. His blood pressure then had not been recorded, but his height was 69.5 inches and his weight, 172 pounds. His father had died of "heart trouble and pneumonia." The patient's past history was irrelevant. He had used tobacco and alcohol moderately. On Feb. 21, 1944, he was admitted to the hospital, having complained for six days of a pressing pain in the anterior thoracic region radiating to the neck and both arms. There had been many attacks of short duration, six of which had lasted five minutes each, accompanied by profuse sweating, pallor, and palpitation. Severe attacks awakened the patient from sleep on three occasions and recurred once while he was walking, once while he was reading, and once while he was taking exercise. Between the attacks, many of which lasted less than a minute, he was comfortable. The entire physical examination was normal, the blood pressure being 130/80 and the pulse rate, 84 per minute. Coronary artery disease or paroxysmal auricular tachycardia was suspected.

The patient was kept at absolute bed rest because of recurring substernal pain lasting four to five minutes and accompanied by sweating. Serial electrocardiograms were made from the first to the eleventh day. These were normal except for minor variations (Fig. 4).

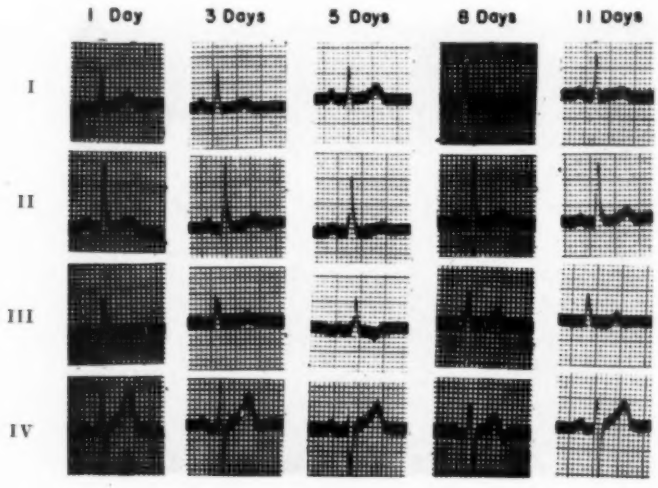

Fig. 4.—Case 327. Survivor, 30 years of age. Electrocardiographic series made during the three weeks of prodromal symptoms.

The course was afebrile and asymptomatic except for the intermittent pains until the seventeenth hospital day when a severe protracted pain developed, with dyspnea, sweating, and pallor. Within thirty-six hours the temperature rose to 101.2° F. and reached normal again by lysis after six days. The blood pressure immediately before the onset of this attack was 130/80; fifteen minutes after the onset it was 160/130; twenty-four hours later, 150/102; and forty-eight hours

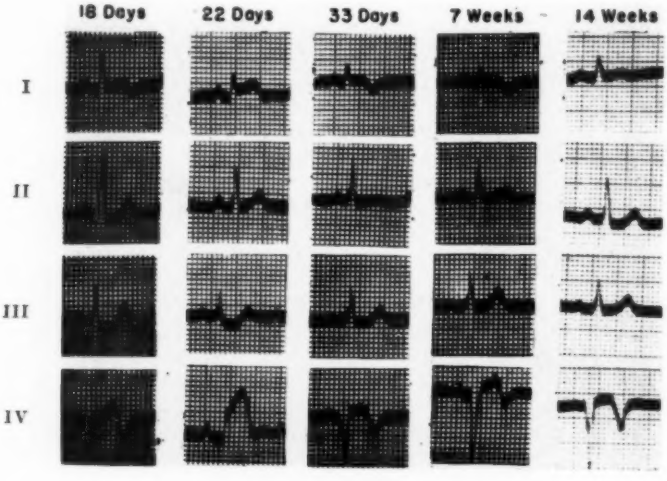

Fig. 5.—Case 327. Electrocardiographic series made during course of anterior myocardial infarction following three weeks of prodromal symptoms (compare with Fig. 4).

later, normal. Repeated white blood cell counts ranged from 8,900 to 6,500 with 68 to 64 per cent polymorphonuclear leucocytes. Many sedimentation rates ranged from 12 to 1 mm. in one hour. A roentgenogram of the chest was negative. A series of electrocardiograms now showed the progressive changes of acute anterior myocardial infarction (Fig. 5). The patient was discharged from the hospital on July 14, 1944, with the diagnosis of acute coronary artery thrombosis with anterior infarction.

The verteran was examined eight months after his discharge from the Army. He had had slight substernal pain and dyspnea on exertion. The physical examination was normal. The blood pressure was 134/92. A roentgenogram indicated that the heart was of normal size and shape. An electrocardiogram was similar to a tracing made during the fourteenth week after the main attack. Since September, 1944, two months after discharge, the veteran had been gainfully employed as inspector of motor vehicle equipment.

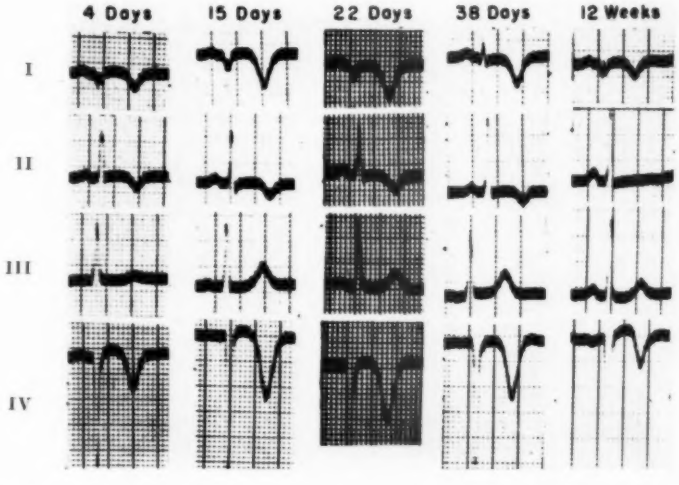

Fig. 6.—Case 34. Survivor, 28 years of age. Anterior myocardial infarction in a Negro.

Case 34 (Acute Anterior Myocardial Infarction in a Negro).—A 28-year-old Negro corporal of the Army Air Force, whose former occupation was that of a hospital attendant, had been inducted into the Army Aug. 3, 1942. His blood pressure then was 108/68, his height, 65 inches, and his weight, 173 pounds. His mother, living, had high blood pressure. His previous history was irrelevant. He used tobacco and alcohol moderately.

The corporal felt well until two days before admission to the hospital, when pain suddenly developed in the left pectoral region and substernal area. On deep breathing, the pain radiated to the neck and left shoulder. It was, at first, "more of an ache than a pain," but it gradually became more severe and agonizing, and marked dyspnea ensued.

On admission, Jan. 30, 1944, he was observed to be very dyspneic and apprehensive and he complained of excruciating pain in the precordium. The heart appeared to be normal, with an occasional premature beat; otherwise the examination was negative. The blood pressure was 135/100, the pulse rate, 96 per minute, and the temperature, 97° Fahrenheit. The clinical impression was that of pleurisy on the left side, but heart disease was to be ruled out.

Shortly after admission the patient vomited. The temperature rose gradually to 102° F. on the third hospital day and three days later declined to normal, where it remained. A transient pericardial friction rub was heard on the fourth and fifth hospital days. After the first day all blood pressure readings were within normal limits. Convalescence was uneventful. The white blood cell counts were 19,000 with 84 per cent polymorphonuclear leucocytes on January 31 and 10,000 with 66 per cent on February 4. The sedimentation rate was 11 mm. on February 4, 8 mm.

on February 14, 11 mm. on February 15, and 4 mm. on two later dates. A series of electrocardiograms gave evidence of acute anterior myocardial infarction, as shown in Fig. 6. Report of a roentgenogram of the chest on February 4 stated, "The heart appears enlarged, with the cardiothoracic ratio well over 50 per cent, and generalized increase in the lung markings throughout." On February 11, report of another film noted: "The heart appears enlarged; it has a hypertensive configuration." The soldier was discharged from the Army on April 20, 1944, with the diagnosis of (1) thrombosis of a coronary artery due to coronary arteriosclerosis and (2) myocarditis, degenerative, chronic, severe, due to the coronary artery disease and preceding thrombosis.

An examination two months after discharge from the Army revealed nothing abnormal, and there had been no symptoms. A roentgenogram of the chest revealed the cardiothoracic ratio to be 52.4. The veteran had completed vocational training as a barber and was planning to open his own shop.

(To be concluded in the November issue. The references will accompany the last section.)

THE EFFECT OF INTRAVENOUS AMINOPHYLLINE ON THE CAPACITY FOR EFFORT WITHOUT PAIN IN PATIENTS WITH ANGINA OF EFFORT

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THE use of aminophylline for the relief of pain due to coronary insufficiency has been the subject of considerable investigation. The pharmacologic evidence that aminophylline is a coronary vasodilator is quite conclusive, but opinion has been divided on its efficacy as a therapeutic measure for the relief of angina pectoris. In 1933, Wayne and Laplace[1] reported that euphyllin (aminophylline) administered intravenously to four patients with the anginal syndrome brought about improvement in only two of them, and that nitroglycerin had a much greater effect. They concluded: "Whatever, therefore, the effect of euphyllin in animal experiments, its action as a coronary dilator is insufficient to recommend its use in angina of effort." In 1937, Gold and co-workers[2] conducted an extended clinical trial of theophylline and aminophylline by mouth in the treatment of cardiac pain, using careful control measures and the "blind" technique. They reported that "patients with cardiac pain are unable to distinguish the effects of a placebo from those of a xanthine when measures are taken to preclude the identification of the agent by any means other than the relief of pain. It is concluded that the xanthines exert no specific action which is useful in the routine treatment of cardiac pain." In 1939, Master and associates[3] reported that oral aminophylline produced improvement in 31 per cent of 127 cases of anginal syndrome and diminished pain 50 per cent of the times it was used. However, since they obtained almost identical results with milk sugar (30 per cent and 52 per cent, respectively), they stated: "obviously one cannot ascribe a specific effect to a drug when its action is no better than that of an inert substance."

In contrast to these unfavorable reports, Brown and Riseman[4] reported in 1937 that of seventeen patients with angina pectoris who were given aminophylline by mouth, 59 per cent were benefited, 12 per cent showing increases of 50 to 100 per cent in exercise tolerance. Massel[5] reported in 1939 that of five patients given eight courses of treatment with aminophylline by mouth, four courses gave relief and four were ineffective. In 1940, Levy and co-workers[6]

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reported a study of the effects of drugs on the anginal syndrome induced by anoxemia and on the electrocardiogram during pain. In ten tests with intravenous aminophylline, they reported a prolongation of 63 per cent in the time of appearance of pain and a diminution of 58 per cent in the RS-T deviations. When aminophylline was given by mouth, it caused a prolongation of 26 per cent in the time of appearance of pain, and the RS-T deviations were diminished by 32 per cent. One year later, Williams and associates,[7] in a similar study, reported that seven patients given 3 grains of aminophylline three times a day, by mouth, showed no significant delay in the onset of pain (8 per cent) and an average diminution in RS-T deviations of 36 per cent. In a group of five patients given 0.48 Gm. of aminophylline intravenously, the onset of pain was delayed 75 per cent and the RS-T deviations were diminished by 49 per cent. In 1941, LeRoy[8] studied sixty-eight patients with angina pectoris and found that 75 per cent were improved by oral aminophylline. In the majority of the cases, the pain was on the basis of syphilitic coronary artery disease; the results are, therefore, not strictly applicable to the usual type of coronary arteriosclerosis.

Boyer,[9] discussing the status of therapeutic claims for aminophylline in 1943, stated that "the mere existence of honest differences in opinion suggests that these drugs may be without specific action in the treatment of cardiac pain." He placed "the burden of proof on those who claim therapeutic efficacy," and suggested that accepted statistical methods be employed to clarify the significance of clinical studies.

In view of these conflicting reports, and with the object in mind of establishing more clearly the status of aminophylline, it was decided to study the effect of the drug when administered intravenously, the test of exercise tolerance being used as the index, according to the method described by Wayne and Laplace.[1] In this method the patient exercises until he develops pain. The method differed from that employed by Riseman in that three successive trials were carried out on the same day, separated by rest periods of one hour, rather than one trial per day on successive days. The three tests were performed on the same day because, in contrast with Riseman, we found considerable variations in exercise tolerance in the same patient on different days. The rest period of one hour was chosen so as to eliminate the beneficial effect of exercise itself upon subsequent tests of exercise tolerance.[1]

All of the subjects were seen in the morning and each period of observation took from three to four hours. Preceding the test, the subject took no breakfast or medication. No sedation was taken the night before the test. Upon arrival, the patient rested for one hour in a comfortable easy chair, during which time frequent pulse and blood pressure determinations were made to provide an index of resting levels. The first test was then carried out by having the subject walk back and forth over a set of steps similar to those described by Master and Oppenheimer[10] until he developed anginal pain similar to his usual attacks in everyday activity. The average rate of walking per minute was determined, and in all subsequent tests on that patient the same rate of walking was maintained. A hinged step with a small mechanical counter attached was used to record the number of trips over the steps.

As soon as the onset of pain occurred, the subject sat down and rested for one hour. A second determination was then made, followed by another rest period of one hour and a third test. That completed the series of trials for any one patient on one day.

The study was conducted by the "blind" method. The materials for injection, 10 c.c. of a 2.4 per cent aminophylline solution and an identical quantity of physiologic saline, were prepared by a nurse, for each day, in identical syringes marked only with code numbers so that the contents were unknown to the observer as well as to the subject. A method was devised for varying the order of the trials (control test without any injection; control test with a placebo injection; and test with an injection of aminophylline) so that all possible combinations of the three tests were used in different sequence. The code numbers on the syringes indicated the order in which the injections were to be given. The contents of the syringes and the corresponding code numbers were noted on cards, sealed in envelopes, and kept sealed until the entire study was completed. Injections were given in a standard manner, starting at ten minutes before each exercise test, and continuing for five minutes (2.0 c.c. per minute); they were followed by five more minutes of rest before the exercise test was started. The first visit of each patient was devoted to control tests and occasionally to check the response to nitroglycerin.

The patients studied were selected from the active census of the cardiac clinic and were all unequivocal cases of arteriosclerotic or arteriosclerotic and hypertensive heart disease with chest pain brought on by exertion and relieved by rest and nitroglycerin. For the purpose of this study, it was decided not to include those patients in whom chest pain also occurred spontaneously at rest, thereby eliminating or minimizing the possibility of accidental end points not related to the exercise tolerance test. Patients receiving digitalis were also omitted because of the reported deleterious effect of digitalis on cardiac pain. Patients receiving diuretics, mercurial or otherwise, or manifesting evidence of cardiac failure were not included. Also excluded were patients who might not be able to perform the tests satisfactorily for other reasons, such as intermittent claudication, arthralgias, and marked obesity. The group that was finally selected provided us, therefore, with suitable indicators of the anginal syndrome, and the number of interfering factors was kept at a minimum.

RESULTS

In all, 124 tests were performed by a total of seventeen patients, but six patients were eliminated after preliminary testing because of failure to elicit an unequivocal end point or because of their inability to carry out the tests properly. In addition, certain tests were not included in the final data because of absence of pain end points in all trials on the day of testing or because of failure to complete the series of three tests on one day. The final data consisted of ninety-nine trials performed by eleven patients of which forty-six were trials without any injection, twenty-two were control trials with placebo injections, and twenty-two were trials following the intravenous injection of 0.24 Gm. of aminophylline. The remaining nine trials were used to check the response to nitroglycerin (Table I).

TABLE I. SUMMARY OF CLINICAL DATA AND RESULTS OF EXERCISE TOLERANCE TESTS

PATIENT	SEX	AGE	DIAGNOSIS	ECG	NUMBER OF TRIPS PERFORMED		
M. S.	M	46	Arteriorsclerosis, coronary sclerosis, old myocardial infarct	Myocardial damage	47(W) 52(W) 113(A)	33(W) 53(S) 65(W)	65(N) 120(A) 86(S)
C. S.	F	51	Arteriosclerosis and hypertension, enlarged heart, dilated aorta	Myocardial damage	15(W) 16(W)	16(W) 14(S)	15(N) 22(A)
H. M.	M	54	Arteriosclerosis and hypertension, coronary sclerosis, myocardial fibrosis	Normal	10(W) 26(A)	6(W) 27(S)	16(N) 29(W)
M. P.	M	52	Arteriosclerosis, old coronary thrombosis, myocardial fibrosis	Myocardial damage	81(W) 104(A) 65(S) 64(W)	96(W) 87(W) 102(A)* 86(S)	70(W) 94(S) 81(W) 102(A)*
M. R.	M	52	Arteriosclerosis and hypertension, enlarged heart, coronary sclerosis	Left ventricular strain	28(W) 26(S) 28(W) 35(A)	34(W) 42(A) 29(S) 35(W)	32(W) 39(W) 42(A) 31(S)
S. P.	M	53	Arteriosclerosis, enlarged heart, coronary sclerosis, myocardial fibrosis	Myocardial damage	7(W) 3(S) 8(W) 7(A)	7(W) 9(W) 13(A) 9(S)	13(N) 8(A) 11(S) 8(W)
S. Z.	M	41	Arteriosclerosis, coronary sclerosis, myocardial fibrosis	Myocardial damage	36(W) 64(A) 60(W) 60(S)	43(W) 80(W)* 61(S) 82(A)*	64(N)* 80(S)* 80(A)* 81(W)*

P. N.	M	64	Arteriosclerosis, old coronary thrombosis, dilated aorta	Myocardial damage	6(W) 11(S)	6(W) 6(A)	4(N) 6(W)
I. K.	M	59	Arteriosclerosis and hypertension, coronary sclerosis, diabetes mellitus		32(W) 24(W)	40(N) 38(A)	26(W) 34(S)
I. D.	M	61	Arteriosclerosis, enlarged heart, coronary sclerosis	Myocardial damage	24(W) 32(W) 42(A)	46(N) 54(A) 37(S)	29(W) 45(S) 43(W)
W. H.	M	56	Arteriosclerosis, enlarged heart, coronary sclerosis	Myocardial damage	9(W) 15(W) 29(A)	34(N) 32(A) 19(S)	15(W) 29(S) 23(W)

*No pain end point.
W = Control (walk, without injection).
S = Saline injection.
A = Aminophylline.
N = Nitroglycerine.

The first comparison of results was made with data obtained from tests in which the trials with saline preceded the trials with aminophylline (Table II). There were ten pairs of results in that sequence, and the differences in performance between the trials immediately following saline and the trials immediately following aminophylline were determined for each individual. The average of these individual differences was 19.8 trips, the standard error being ± 6.3 ($t = 3.14$; $p = 0.01$).

TABLE II. EXERCISE TOLERANCE WHEN TRIALS WITH SALINE PRECEDED TRIALS WITH AMINOPHYLLINE

PATIENT	NUMBER OF TRIPS		
	SALINE	AMINOPHYLLINE	DIFFERENCE
M. S.	53	120	67
C. S.	14	22	8
M. P.	65	102	37
	86	102	16
M. R.	26	42	16
	29	42	13
S. P.	3	8	5
S. Z.	61	80	19
	60	82	22
P. N.	11	6	−5
Average			19.8

A similar comparison was then made with the data obtained from tests in which the order was reversed, the trials with aminophylline preceding the trials with saline (Table III). There were twelve pairs of results in that sequence. The differences in performance were determined for each individual, and the

TABLE III. EXERCISE TOLERANCE WHEN TRIALS WITH AMINOPHYLLINE PRECEDED TRIALS WITH SALINE

PATIENT	NUMBER OF TRIPS		
	AMINOPHYLLINE	SALINE	DIFFERENCE
M. S.	113	86	−27
H. M.	26	27	1
M. P.	104	94	−10
M. R.	35	31	−4
S. P.	13	11	−2
	7	9	2
S. Z.	64	80	16
I. K.	38	34	−4
I. D.	54	45	−9
	42	37	−5
W. H.	32	29	−3
	29	19	−10
Average			−4.6

mean difference was found to be 4.6 trips more for aminophylline than for saline (standard error, ±2.9). Since t in this series is 1.6, this difference is not significant.

Whether saline injection alone produces any increase in the capacity for effort, through suggestion or other means, was not determined because the number of suitable tests for such a comparison was too small.

DISCUSSION

The literature on the effect of aminophylline on the capacity for effort without pain in patients with angina of effort is conflicting. While there seems to be little doubt that aminophylline is a coronary vasodilator, there is considerable doubt as to whether the usual oral doses are absorbed in sufficient concentration to prove of significant value in the treatment of the angina of effort. There seems also to be some doubt concerning the effectiveness of the coronary vasodilatation after intravenous injection, and it is in relation to this problem that the foregoing experiments were planned. In a series of experiments on patients with unequivocal angina of effort, so planned as to eliminate conflicting factors in the interpretation of the results, it was found that an intravenous injection of 0.24 Gm. of aminophylline increases the capacity to walk steps without pain. The statistical analyses of the data leave little doubt that the effect of aminophylline obtained in these experiments is a significant one. There were two sets of data, one in which the sequence of comparisons was saline-aminophylline, and the other in which the sequence was reversed, aminophylline-saline. It is of interest to note that the highly significant difference between saline and aminophylline which appeared in the first series of experiments was absent when the sequence was reversed, adding further weight to the observation that intravenous aminophylline exercises a specific effect in increasing the capacity for effort without pain, an effect which lasts longer than one hour since it was still present when the subsequent experiments with saline were performed.

The question of the practical significance of the foregoing observations is a matter of some interest; therefore, it is important to translate the statistical significance into practical terms. The increase of 19.8± the standard error of 6.3 trips, or 48± 16 per cent, over the performance with saline alone means that the chances that there is a real increase in performance are quite high, namely, about 99 out of 100. This does not, however, imply anything about the magnitude of the percentile increase. It may be anywhere from 1 to 96 per cent (mean ± three times the standard error). If we wish to attribute an actual value to the magnitude of this increase, the chances that we are correct in assigning such a value are not so high. For example, we can only be certain to the extent of about 95 out of 100 chances that the increase is at least 16 per cent (mean minus two times the standard error). And we can have practically no assurance, only about two chances out of three, that the increase is at least 32 per cent (mean minus one standard error). In other words, we are very certain that there is an increase in performance; we are fairly certain that the increase is about 16 per cent; we are not at all certain that the increase is any more than 16 per cent.

It should not be inferred, therefore, that the results obtained in these experiments justify the free use of aminophylline by oral administration or even by intravenous injection for the relief of effort angina. Nitroglycerin, taken sublingually, is a very effective method of obtaining coronary vasodilatation and increased capacity for effort without pain, and a tablet taken under the tongue is more convenient than an intravenous injection. The question remains as to which of these measures produces a greater effect and one of longer duration. This question is the subject of an investigation now under way.

SUMMARY

1. An intravenous injection of 0.24 Gm. aminophylline increases the capacity for effort without pain in patients with angina of effort. There are fairly marked individual variations in this response.

2. The increased capacity for effort without pain lasts longer than one hour.

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I. CORRELATION OF ELECTROCARDIOGRAPHIC AND PATHOLOGIC FINDINGS IN ANTEROSEPTAL INFARCTION

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THORACIC leads were utilized by Waller[1] in 1887 in connection with the capillary electrometer and were employed by Einthoven[2] prior to development of the string galvanometer. For more than twenty years after the application of the latter to clinical electrocardiography, it was standard practice to take merely the three limb leads recommended by Einthoven. During this period, however, direct epicardial and precordial leads were employed experimentally, notably by Lewis and co-workers in their studies of auricular flutter,[3] and by Wilson and associates in their studies of right and left ventricular potentials in normal animals[4] and in bundle branch block.[5] In 1930, Wilson[6] predicted the value of precordial leads in coronary occlusion and, with his associates, undertook a comprehensive study which extended over a period of several years.

Widespread clinical interest in precordial leads was awakened in 1932 by the report of Wolferth and Wood.[7] Their demonstration that certain anterior infarcts produced RS-T displacement in tracings taken through a precordial electrode, but not through extremity leads, has been amply confirmed. Following this report, it became customary in most clinics to supplement the three limb leads with a single precordial lead, usually applied in the vicinity of the apex, less commonly in the fourth intercostal space at the left sternal border, or at other sites. Nevertheless, the inadequacy of a single precordial lead, regardless of the point of application of the exploring electrode, has gradually become apparent, partly as a result of studies correlating electrocardiographic and pathologic findings. From the more extensive reports[8-12] a number of cases may be collected in which anterior infarction, not diagnosable from the four-lead electrocardiogram, was demonstrated at autopsy. On the other hand, patterns in Lead IV simulating those of anterior infarction were found in cases where the diagnosis was subsequently excluded at autopsy.[9,12]

Through a series of studies on dogs before and after coronary ligation, Wilson and associates[13-18] demonstrated the close correlation between the QRS-T pattern in multiple epicardial leads and the distribution of the infarct at autopsy. These studies form the basis for the utilization and interpretation of multiple

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precordial leads in human myocardial infarction and consequently will be briefly summarized.

In the characteristic lesion produced by ligation of a major coronary vessel, three concentric zones were distinguished pathologically: (1) a central zone of transmural infarction, extending through the entire wall from endocardium to epicardium; (2) a marginal zone of infarction confined to a portion of the wall, most commonly the subendocardial layer; and (3) an outlying zone of ischemia manifested by pallor and by absence of histologic evidence of degeneration. In smaller lesions, produced by ligation of secondary or tertiary branches, only the marginal and ischemic zones were represented.

The typical electrocardiographic pattern registered through direct epicardial leads from the central zone consisted of a QS complex with smooth descending and ascending limbs.[15] This QS deflection simulated the record obtained through an electrode inserted into the left ventricular cavity[13,14] and was attributed to transmission of cavity potentials to the surface through an infarct which, like a valvular orifice, behaved merely as a conducting window. The T wave in direct epicardial leads also resembled that recorded from the ventricular cavity when the intervening myocardium was completely destroyed.[17] On the other hand, a markedly elevated RS-T junction and monophasic upright T wave were obtained when the subepicardial muscle was acutely injured, but not dead. A notched rather than a smooth QS complex was the characteristic finding when a small portion of the underlying myocardium was spared.[15] The upstroke of the notch represented positive potentials momentarily referred to the epicardium as a result of activation of the remnant of responsive muscle.

The usual finding in epicardial leads from the marginal zone consisted of an abnormal QR complex,[16,17] which could be correlated with infarction of the subendocardial layer and preservation of the subepicardial layer of muscle. The initial Q represented negative cavity potentials transmitted to the surface during the time when the impulse traversed or circumvented the infarcted subendocardial muscle, and the succeeding R represented positive potentials referred to the surface as soon as the impulse reached and began to activate the intact subepicardial layer. An abnormally small initial R was recorded in direct leads when the infarct extended in patchy fashion through the underlying wall or when it was confined to the subepicardial layer.[16] The typical finding in epicardial leads over the ischemic zone consisted of a normal QRS and cove-shaped inversion of the T wave.[17] By means of multiple direct leads, it was thus possible to demarcate accurately the boundaries of an infarct and to gauge the thickness of the wall involved.

The major difference between the QRS-T contour in direct and that in precordial leads was referable to the fact that the tracing obtained through the latter was dominated by the potential variations of a much larger surface of epicardium than that obtained by the former.[18] In the presence of a large central zone of uniform transmural infarction, an overlying precordial lead revealed a QS complex comparable in shape to that obtained through direct leads from the subjacent epicardium. When the central zone was small, precordial leads tended to show a notched QS complex or a QR deflection due to

admixture of effects from the central and marginal zones.[16] While a sharp delineation between central, marginal, and ischemic zones could be made out in direct leads, a more gradual transition was found in precordial leads as a result of overlapping effects. Nevertheless, the data furnished by multiple precordial leads in experimental anterior infarcts in animals appeared to provide sufficiently accurate localization for clinical purposes.

The Wilson group introduced precordial leads V_1 through V_6 and unipolar extremity leads V_R, V_L, and V_F and have subsequently published detailed accounts[18,19] of the findings in these leads associated with infarcts in various locations. Their clinical deductions were confirmed in a few cases which came to autopsy. Kossmann and De La Chapelle[20] noted a close correspondence between the QRS-T pattern in the Wilson precordial and extremity leads and the findings at autopsy in a series of nine cases. Because of the very small number of reported cases with pathologic confirmation of the infarct diagnosed with the aid of multiple precordial leads, there appeared to be a need for an extensive study.

A correlative study of electrocardiographic and pathologic findings has been made in a total of 161 cases of myocardial infarction established at autopsy during a four-year period beginning in July, 1943. One or more electrocardiograms, consisting of precordial leads V_1, V_2, V_3, V_4, V_5, and V_6 and the standard limb leads, were obtained in every case, and the augmented unipolar limb leads were taken in 157 cases. All of our cases in which the foregoing twelve leads were available and in which myocardial infarction was definitely established and accurately localized at autopsy during the specified period are, with six exceptions, included in the series. These cases were omitted because the last electrocardiogram was taken some time before death and autopsy revealed merely a terminal infarct, which, from its pathologic characteristics, had unquestionably occurred after the last electrocardiogram had been obtained. Whenever there was doubt as to whether the electrocardiogram had been taken before or after the development of the infarct, the case was included in the series. A number of cases in which the precordial electrocardiogram was limited to Leads V_2, V_4, and V_6 were automatically excluded by this method of selection.

The method of clinical and pathologic study has been described in detail in a previous communication.[21] Post-mortem examination included injection of the coronary arteries with radiopaque mass, roentgenogram, and subsequent dissection with multiple transmural microscopic blocks in 152 of the 161 cases. The position of the infarct, as determined by inspection, was outlined on the roentgenogram with wax pencil and was corrected, when necessary, to conform with the microscopic findings. In some cases the infarct was delineated roentgenographically by its avascularity, but in many cases vessels within the infarct were filled with a radiopaque mass. In some of the latter, the vessels had undoubtedly carried blood prior to death, but in others, an ante-mortem thrombus may have been dislodged by forceful injection of the lead-agar mixture from a hand syringe. This did not detract from the objectives of the pathologic study, which were to determine the presence or absence of infarction,

to demarcate accurately the position of the myocardial lesion, and to estimate its age. No particular effort was made to trace the relation of the infarct to muscle bundles, as described by Robb and Robb[22] and by Lowe,[23] since in our experience the infarct usually involved more than one muscle bundle. The age of the infarct was determined from the criteria of Mallory and co-workers,[24] modified somewhat by our own experience.

In the presentation of our data, a detailed analysis has been made of the electrocardiogram of each individual case, independent of the pathologic findings, and subsequently an attempt has been made to correlate the findings in the various leads with those observed at autopsy. The anatomic location and age of the infarct have been described as briefly but as accurately as possible and illustrated, when necessary, by a reproduction of the roentgenogram. In order to save space, the pathologic criteria upon which the diagnosis of infarct was established and the age estimated are not included, but will be reserved as a subject for a separate communication. Furthermore, description of the pathologic findings pertaining to the coronary vessels is also omitted, since the electrocardiographic abnormalities are a direct manifestation of the secondary changes in the myocardium rather than the primary changes in the coronary arteries.

In spite of the foregoing curtailment, the data are too voluminous for condensation into a single manuscript. The cases have been classified into the following seven groups, according to the location of the infarct at autopsy, namely: anteroseptal, large anterolateral, anteroposterior, septal, posterior, posterolateral, and lateral. Considerable overlapping is unavoidable in any classification because of the frequency of two or more infarcts at autopsy and because of the tendency of large anterior infarcts to extend into the septum, the lateral wall, and around the tip of the ventricle to the posterior aspect of the apex, and the similar tendency of large posterior infarcts to extend into the septum and lateral wall. When the infarct could be classified anatomically into more than one category, the lesion of principal electrocardiographic interest became the determining factor.

Regardless of the category in which an individual case is classed, the discussion of the electrocardiographic-pathologic correlation covers all ramifications of the infarct.

In this communication, an analysis is presented of the electrocardiographic and pathologic findings in twenty cases of anteroseptal infarction. Wilson and associates[18,19,25] have utilized this term for electrocardiograms with diagnostic QRS abnormalities in one or more of the first four precordial leads, but not in V_5, V_6, or the standard leads. Our classification was based primarily on the autopsy findings. In the majority of our twenty cases, the infarct was limited to a relatively narrow strip of the free anterior wall of the left ventricle and the contiguous anterior portion of the interventricular septum and did not extend into the lateral or posterior aspect of the left ventricle. The remainder had a more extensive infarct or a multiple infarct, but were included because the lesion of principal electrocardiographic interest was in the anteroseptal wall of the left ventricle.

CASE REPORTS

CASE 1.—A woman, 49 years of age, was first hospitalized in August, 1943, for the control of diabetes mellitus complicated by hypertension. She was readmitted on Nov. 18, 1943, with a history of repeated vomiting for one week and with evidence of moist gangrene of both feet. She received a single dose of 20 units of regular insulin at 8:00 P. M. and three hours later was found in circulatory collapse with a blood pressure of 90/60. The infection was not controlled and death occurred in hyperpyrexia on November 21. No cardiac glycosides were given.

Electrocardiographic Findings.—Electrocardiograms obtained on November 19, twelve hours and eighteen hours after the onset of shock, are reproduced in Fig. 1 along with a record taken on the first admission. In the tracing of August 10, the abnormally late onset of the intrinsicoid

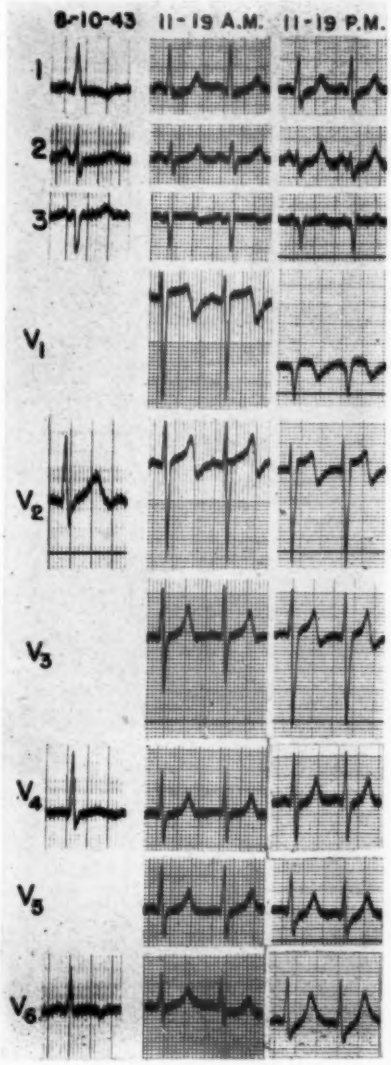

Fig. 1.—Serial electrocardiograms of Case 1 before and after development of high anteroseptal infarction.

deflection in leads over the left ventricle (0.06 second in V_4), the depression of RS-T_1, and the inversion of the T wave in Lead V_6 and Lead I were considered diagnostic of left ventricular hypertrophy. The transitional zone was apparently displaced to the right of Lead V_2. An RS complex was recorded in Lead V_1 on the morning of November 19 and was replaced by a much smaller QS complex in the afternoon. Both tracings were taken in the same posture with similar standardization, and the differences were probably not due to technical errors, since the C_1 position can be accurately located anatomically. For the same reasons, the 50 per cent reduction in the R wave in Lead V_2 was considered significant. In Lead V_1, there was a distinct change from a concave upward RS-T segment and diphasic T wave in the morning tracing to a convex upward RS-T segment and completely inverted T wave in the afternoon. The RS-T junction became more elevated in V_2 and V_3, and the terminal portions of the T waves in these leads became more inverted during the course of the day. The foregoing serial changes in the RST-T complex in Leads V_1, V_2, and V_3 were compatible not only with recent high anteroseptal infarction, but also with acute right ventricular dilatation. Since the QRS changes in Leads V_1, V_2, and V_3 pointed definitely toward the former, an ante-mortem diagnosis was made of a recent infarct localized high in the anteroseptal wall of the left ventricle. The relatively sharp peaking of the T waves raised the question of hyperpotassemia, but this was considered unlikely because the base of the T waves was much broader than is characteristically found. Although the blood potassium was not determined, an elevation sufficient to cause electrocardiographic changes was unlikely, in view of the fact that the blood urea was only moderately elevated to 73 mg. per cent. During the course of the observations on November 19, the RS-T junction in Leads V_4, V_5, and V_6 became depressed. The question arose as to whether this depression was representative of an acute lesion in the subendocardial layer of the anterolateral aspect of the left ventricle or whether it was reciprocal to a coexistent posterior infarction. Although the small initial R_3 disappeared in the afternoon tracing and R_2 became smaller, no elevation of the RS-T segment developed in these leads. Thus, the changes in the standard leads were inconclusive. Unfortunately neither aV_F nor esophageal leads were obtained in this case.

Pathologic Findings.—The heart weighed 480 grams and showed moderate left ventricular hypertrophy. There was no evidence of right ventricular dilatation nor of a pulmonary lesion sufficient to cause acute cor pulmonale. Although not distinctly made out by inspection, a recent patchy infarct was clearly defined microscopically high in the anteroseptal wall of the left ventricle, as demarcated by solid lines in Fig. 2, and a second similar lesion was found at the junction of the lower and middle thirds of the posteroseptal aspect of the left ventricle, as indicated by the broken lines. The patchy anteroseptal infarct was considered responsible for the QRS-T changes in Leads V_1, V_2, and V_3. In the light of our experience with subsequent cases, the developing QS in V_1 and diminishing R in V_2 could be explained best by extension of the anterior infarct into the adjoining septum. The initial R registered in leads over the normal right ventricle is due largely to septal activation[27] and tends to be reduced or eliminated when the septum is infarcted. There was no gross evidence of septal infarction, but the possibility was not excluded, because no microscopic blocks were taken through the septum. Since there was no evidence of a lesion of the apical two-thirds of the anterolateral wall of the left ventricle, the RS-T depression in Leads V_4, V_5, and V_6 was most likely reciprocal to the recent posterior infarction.

CASE 2.—A man, 52 years of age, gave a four-year history of intermittent pain in both wrists, radiating to the shoulders, brought on by exertion and relieved by rest. Since July, 1942, the pain had extended into the chest to reach the sternum. He was first admitted on Nov. 25, 1942, ten hours after the onset of a very severe constrictive retrosternal pain. The hospital course was uneventful, but angina pectoris recurred after resumption of activity. He was awakened by a second severe attack of viselike retrosternal pain on July 26, 1943, and died ten hours later. No cardiac glycosides were given.

Electrocardiographic Findings.—Electrocardiograms selected from a series obtained over an eight-month period are reproduced in Fig. 3. The QS complex consistently present in Lead V_2, together with the classical serial changes in the RS-T segment and T wave of this lead, was diagnostic of anteroseptal infarction. In the first four records of V_4, the deepening T wave, together

with the preservation of a normal initial R, suggested that this lead was reflecting potential variations of an outlying ischemic zone; however, the appearance of a minute Q wave and reduction of the R in later tracings could have been due to the development of a patchy infarction in the subjacent wall or might have been merely due to a slight difference in the position of the electrode with reference to the heart. The tracing of July 26, 1943, was obtained nine hours after the onset of the second attack of pain. From the appearance of a Q_3 together with a markedly elevated RS-T_3, a diagnosis of recent posterior infarction was made. The acute RS-T depression

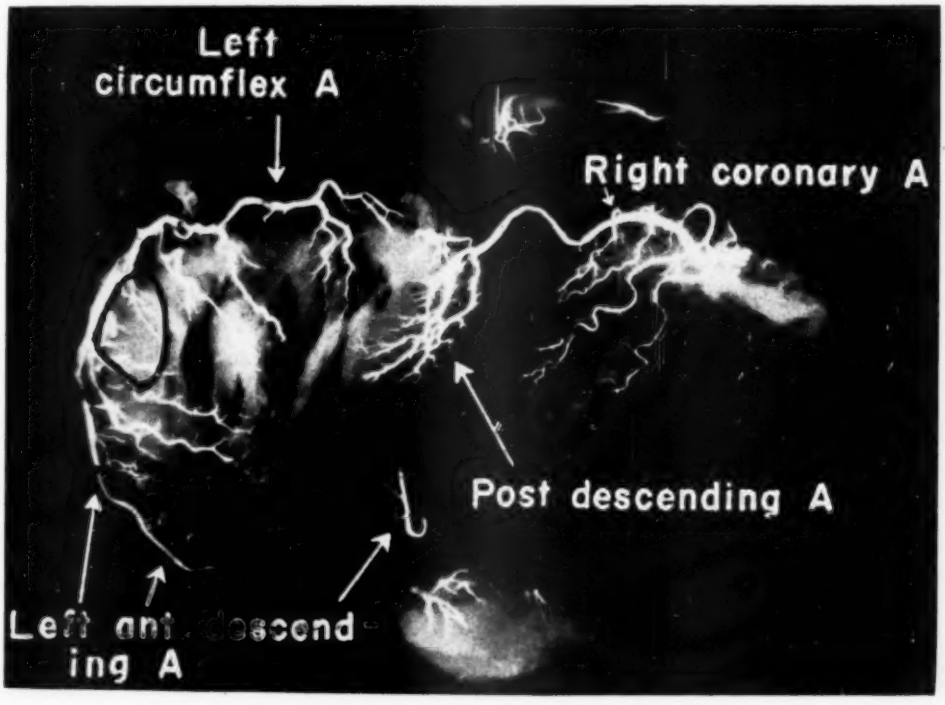

Fig. 2.—Roentgenogram of the heart of Case 1 injected with radiopaque mass and opened by the Schlesinger technique.[27] The recent anteroseptal infarct is demarcated by a solid line and the posteroseptal by a broken line. To assist in orientation in this and all future illustrations in which the Schlesinger technique was used, the arrangement of the heart will be described and anatomical landmarks identified. A longitudinal incision was made through the anterior margin of the right ventricle at its junction with the septum, the latter was removed, and the heart was unrolled and laid flat on the roentgen cassette. The roentgenographic illustrations are arranged with the left ventricle on the reader's left. its anteroseptal margin along with the anterior descending coronary artery forming the left border of the image. When the anterior descending coronary artery continued around the tip onto the posterior aspect of the apex, it was usually severed at the apex by this method of sectioning. The posterior ascending portion of this vessel marked the approximate boundary between the posterior apical aspects of the left and right ventricles, as is evident in Fig. 2. The posterior boundary between right and left ventricles is also indicated by the posterior descending coronary artery and by the sharp difference in density of the ventricular walls. The common origin of the anterior descending and circumflex branches of the left coronary artery is located near the upper left-hand corner of the cardiac image and the origin of the right coronary artery appears near the upper right-hand corner. The course of the left circumflex artery from the anterior to the posterior portion of the groove between the left ventricle and atrium is thus directed from the reader's left toward the center of the cardiac image, whereas the course of the right coronary artery from the anterior to the posterior portion of the groove between the right ventricle and atrium is thus directed from the right toward the center of the roentgenogram. The inferior border of the left ventricular image consists of the anteroseptal portion of the apex on the left, then the lateral, and then the posterior aspects of the apex. The inferior and right borders of the right ventricular image are made up of the severed anteroseptal margin of the right ventricle and the pulmonary artery.

which had developed in Leads V_5 and V_6 was most likely reciprocal to the posterior infarction, but could have been due to extension subendocardially into the lateral wall. Although the T waves had become upright in Leads V_1, V_2, and V_3, the persistence of a QS pattern in these leads was indicative of the old healed infarct of the free anteroseptal wall of the left ventricle and the adjoining interventricular septum.

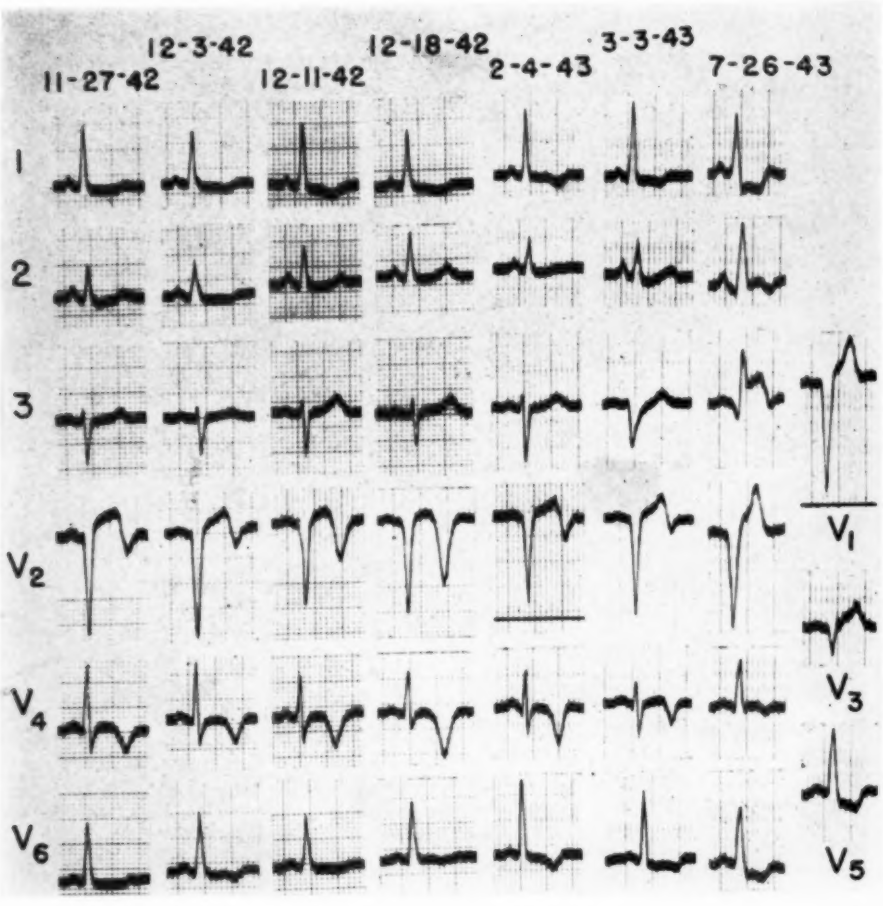

Fig. 3.—Serial electrocardiograms in Case 2.

Pathologic Findings.—The heart weighed 470 grams and exhibited a well-vascularized transmural infarct, involving the apical two-thirds of the anteroseptal wall of the left ventricle, as outlined in Fig. 4, and extending into the contiguous anterior portion of the interventricular septum. The QS complexes in Leads V_1 and V_2 were probably a manifestation of infarction of the anterior portion of the septum. The minute terminal R which followed the deep Q of V_2 was probably derived from preserved subepicardial muscle found in some sections taken through the infarct of the anterior wall. Since the infarct extended to the apex of the anteroseptal aspect of the left ventricle, more definite QRS abnormalities might have been expected in V_4. The ischemic zonal pattern usually recorded in this lead may have been due to counterclockwise rotation sufficient to permit reference of the potential variations of the uninfarcted anterolateral wall to the midclavicular line. The right coronary artery was occluded by a fresh ante-mortem

thrombus at the point marked by an arrow in Fig. 4. Although a number of sections were taken from the posterior walls of the right and left ventricles, no definite evidence of recent posterior infarction could be found. The fact that death occurred ten hours after the onset of pain may account for the lack of histologic change. This case constitutes an example of the electrocardiographic changes preceding the histologic evidence of infarction.[28] There was no histologic evidence of infarction of the lateral wall. The question was left unsettled as to whether the acute RS-T depression in Leads V_5, V_6, and I was reciprocal to the elevation in Lead III or whether it was due to an acute lesion of the subendocardial portion of the lateral wall too early to be recognizable histologically.

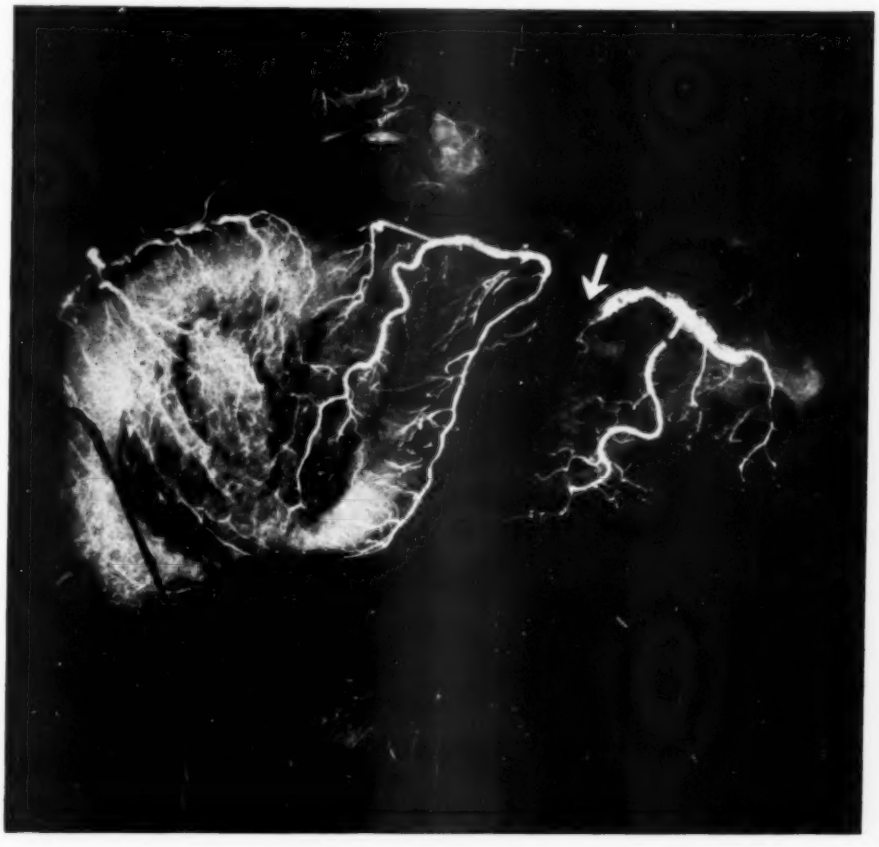

Fig. 4.—Roentgenogram of the injected heart of Case 2.

CASE 3.—A man, 50 years of age, was first hospitalized in August, 1940, because of the recent onset of angina pectoris complicated by congestive failure. He was readmitted in May, 1944, because of recurrent cardiac failure and responded satisfactorily to digitalis. On June 8, 1945, he was suddenly seized with a much more severe and protracted retrosternal oppression accompanied by dyspnea. He was hospitalized for a third time and, on that occasion, there were definite clinical signs of infarction. The daily maintenance dose of 0.1 Gm. of digitalis which he had been taking prior to admission was continued throughout his hospital stay and after discharge. He had no further episodes of protracted retrosternal pain and died on March 25, 1946.

Electrocardiographic Findings.—Electrocardiograms selected from a series taken over a period of one and one-half years are reproduced in Fig. 5. The three standard leads and Lead

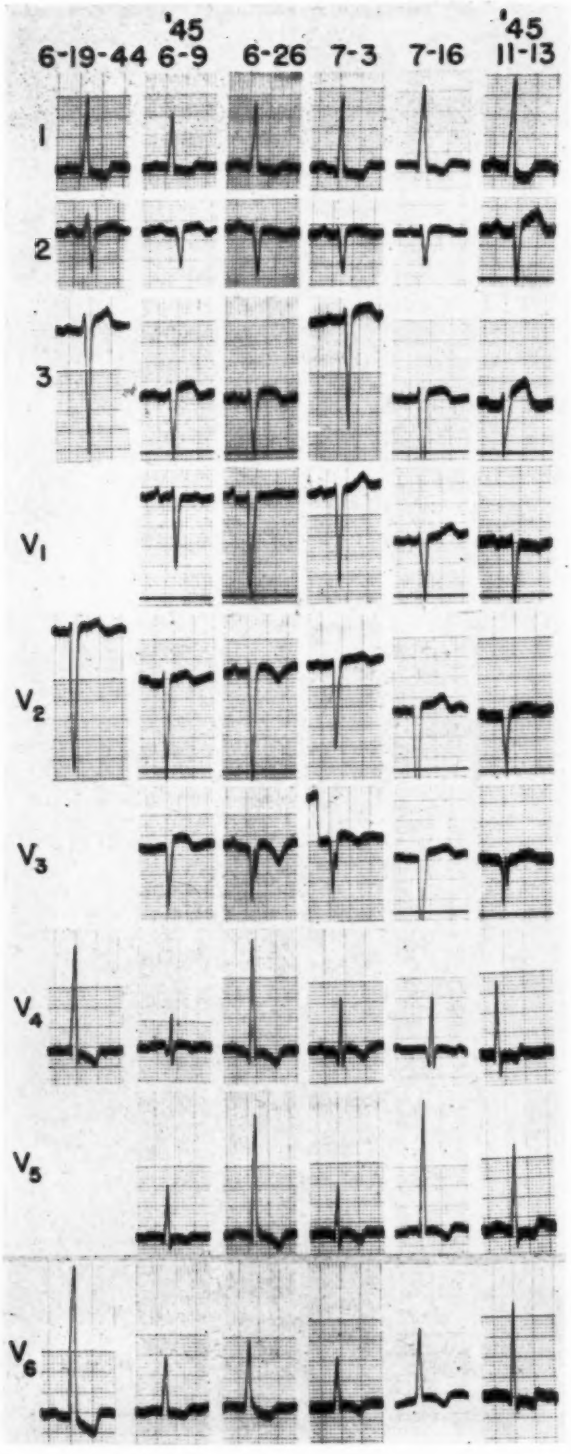

Fig. 5.—Serial electrocardiograms before and after the development of anteroseptal infarction in Case 3.

IVF obtained in August, 1940, were closely comparable to the standard leads and V_4 of June 19, 1944, and consequently were not reproduced. The tall R and slightly delayed intrinsicoid deflection in left ventricular Leads IVF, V_4, and V_6 were attributed to left ventricular hypertrophy; however, a small anteroseptal infarct was not excluded because Lead V_3 was not obtained. The QS complex in V_3 of all tracings taken during 1945 was indicative of anteroseptal infarction, particularly when considered in conjunction with the distinct initial R in V_1 and the smaller R in V_2. The abnormal reduction in the voltage of the R wave in V_2 suggested that this lead reflected the potential variations of a marginal zone of patchy infarction. The serial changes in the RS-T segment and T wave of Lead V_3 during June and July, 1945, were indicative of an organizing infarct. Although the T wave in V_3 later became upright and practically normal in contour, the slurred, notched, or W-shaped QS persisted in this lead as a remnant of the healed anteroseptal infarct. Lead V_4 of the tracings of June 9, July 3, and July 16 displayed a notched or slurred Q wave 0.04 second in duration* and 25 to 33 per cent of the amplitude of the succeeding R. This pattern was attributed to infarction of the subendocardial layer of the anteroapical portion of the left ventricle. The variations on June 26 and November 13 were probably due to a slightly different position of the electrode. The shifting in relationship of electrode to heart on these dates was borne out by the fact that the tracing of June 26 was the only one with an inverted T in V_2 resembling the inverted T of V_3, whereas that of November 13 was the only record with a QS in V_2 comparable to that consistently present in V_3. Leads V_5 and V_6 and the standard leads showed a pattern compatible with left ventricular hypertrophy, but not diagnostic of infarction. Characteristic digitalis effects were present on June 19, 1944, and Nov. 13, 1945.

Pathologic Findings.—The heart weighed 500 grams because of left ventricular hypertrophy. An old healed anteroseptal infarct was found, reaching the apex and extending 6.0 cm. toward the base. The infarct continued into the adjoining septum, but did not involve the lateral wall. The position of the infarct was essentially the same as that in Case 2 (Fig. 4). There was good correlation between the position of the infarct in the anteroseptal portion of the free wall of the left ventricle and the abnormally reduced initial R in V_2, the notched QS in V_3, and the abnormal QR in V_4. The extension of the infarct into the septum had not produced diagnostic changes in Lead V_1. The absence of infarction of the lateral wall was consistent with the premortem ascription of the abnormalities in Leads V_5 and V_6 to left ventricular hypertrophy.

CASE 4.—A man, 58 years of age, a chronic alcoholic, had had hypertension since 1941, intermittent claudication and angina pectoris since 1942, and was first admitted on Oct. 20, 1944, because of severe paroxysms of nocturnal dyspnea and associated retrosternal oppression during the two preceding nights. On the basis of clinical observations in the hospital, recent myocardial infarction was considered unlikely, but could not be definitely excluded. On June 29, 1945, he had an attack of exceptionally severe and protracted retrosternal oppression which led to hospitalization for the next two months. From the clinical course and laboratory findings, a diagnosis of myocardial infarction was made. He was readmitted on Nov. 1, 1945, because of hemiplegia and died three weeks later of bronchopneumonia.

Electrocardiographic Findings.—Electrocardiograms from each of his three admissions are reproduced in Fig. 6. The tracing of Oct. 20, 1944, was obtained thirty-three hours after the first attack of paroxysmal nocturnal dyspnea and before the administration of any cardiac glycosides. This tracing showed a P-R interval of 0.12 second, QRS slurring in the three standard leads, a 0.5 mm. initial R and an exaggerated S wave in Leads V_1 and V_2, and a prominent R wave with slightly delayed intrinsicoid deflection in V_6. The QRS pattern in the precordial leads strongly suggested left ventricular hypertrophy. There was abnormal RS-T depression in Leads V_5 and V_6, but the T waves were upright in all leads and were of relatively high voltage in Leads V_2, V_3, V_4, and V_5. The RS-T depression could have been the result of uncomplicated left ventricular hypertrophy, but was also compatible with a small subendocardial anterolateral infarct. Because of persistent left ventricular failure, digitalis was started on Oct. 22, 1944, and a

*Measurements of the duration of the Q wave represented the time interval elapsing between its onset and nadir, whereas the duration of R represented the time interval from the beginning to the peak of the upstroke.

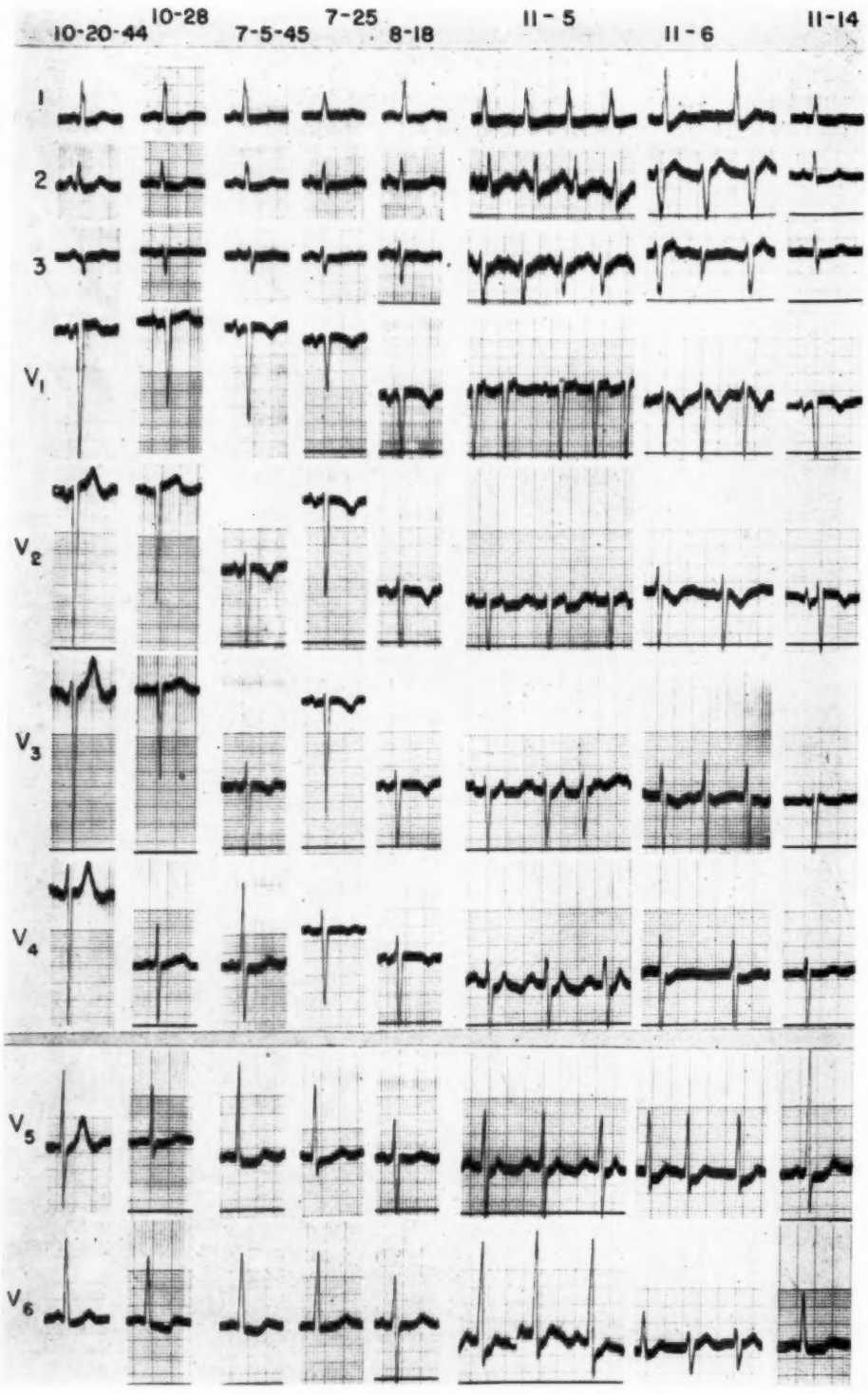

Fig. 6.—Serial electrocardiograms in Case 4.

total of 2.0 Gm. was given prior to the next electrocardiogram on October 28. Since the changes in the RS-T junction and T waves could have been the result of the digitalis, the question as to whether a small infarct had occurred was left unsettled. An unreproduced tracing taken on June 30, 1945, twelve hours after the onset of the pain which led to his second admission, was similar to that of July 5, 1945, except for the presence of upright T waves in Leads V_2 and V_3. The abnormal depression of the RS-T junction in Leads V_4, V_5, and V_6 on June 30 and July 5, 1945, gradually disappeared during the next six weeks. The T waves in Leads V_2 and V_3 became sharply inverted between June 30 and July 5 and remained so throughout the hospital stay. A QS complex was present in Lead V_1, but no abnormal Q waves were found in any precordial or extremity lead. Since no cardiac glycosides were administered during his second hospitalization, a subendocardial anterolateral infarct was considered the most likely cause of the RS-T abnormalities in Leads V_5 and V_6. The T-wave inversion in Leads V_2 and V_3 might have been due to a small intramural anteroseptal infarct, to acute right ventricular dilatation, or to localized pericarditis, but the first alternative was favored because of the late development and persistence of the findings. It is noteworthy that serial records of the standard leads gave no evidence of either infarct. The tracing of November 5, which was taken before the administration of cardiac glycosides, revealed an auricular tachycardia with variable block. On November 6, following the administration of 1.6 Gm. of Cedilanid, a transient auricular fibrillation with ventricular extrasystoles developed and sinus rhythm was then restored. From the contour of the RS-T segments and shortening of the Q-T interval, it is probable that the RST-T changes were due to Cedilanid. Attention is drawn, however, to the fact that the R wave in V_3 of November 14 was smaller than that of V_2. This might have been a remnant of the earlier anteroseptal infarction.

Pathologic Findings.—The heart weighed 577 grams and showed rather marked left ventricular hypertrophy. Gross inspection revealed two separate areas of scarring, as demarcated in Fig. 7. One of these lay intramurally in the anteroseptal aspect of the second and third segments from the apex; the other occupied the subendocardial one-third of the anterolateral aspects of the third and fourth segments. By microscopic examination, these were regarded as healed infarcts of several months' duration. From the electrocardiograms, it is probable that the anteroseptal infarct occurred in July, 1945. The fact that the infarct was limited to the mid-portion of the wall is in keeping with the absence of Q waves and the isolated T-wave abnormalities. The subendocardial anterolateral infarct could have occurred on either the first or second admission, but more likely at the latter time because of the more typical changes in the RS-T segment. The absence of abnormal Q waves in Leads V_5 and V_6 may have been due to the relatively small size of the infarct in comparison with the bulk of the surrounding uninfarcted muscle.

CASE 5.—A hypertensive man, 72 years of age, was admitted in coma following a cerebral hemorrhage. His blood pressure on the day of admission ranged from 240/110 to 300/150. During the second night of hospitalization, peripheral circulatory collapse developed and the blood pressure fell to 140/70. The patient did not regain consciousness and died forty-seven hours after admission from the cerebral vascular accident.

Electrocardiographic Findings.—An electrocardiogram taken after the administration of 0.8 mg. Cedilanid and eight hours before death is reproduced in Fig. 8,*A*. Close scrutiny of Lead V_1 revealed a Q wave 0.5 mm. deep followed by a 1.5 mm. R wave and a notched S wave 10 mm. deep. Although a QS deflection may occur as a normal variant in V_1, a Q preceding an RS complex is abnormal and is representative of septal infarction. Lead V_2 exhibited a QS complex with a coarse notch near the base of the descending limb. This finding, taken in conjunction with the pattern in V_1, was attributed to infarction of the septum and adjoining anteroseptal wall at the base of the left ventricle. The RS-T junction was depressed in V_1 and V_2 and the segment sloped straight downward in a manner suggestive of digitalis effect. In view of the fact that the Q-T interval was at the upper limits of normal (0.32 second at a rate of 110 per minute), it was believed that the administered Cedilanid was not the major cause of the changes in the RS-T segment and T wave. The depression of the RS-T junction and contour of the segment were strongly suggestive of the changes produced by acute infarction confined to the subendocardial layer. In Lead V_3 there was a 2.5 mm. Q wave, followed by R and S waves, each of 15 mm., and by a

sharply inverted T wave. Since the Q decreased and then disappeared in leads farther to the left, the Q in V_3 was regarded as abnormal and referable to a thin marginal zone of subendocardial infarction. The tall R and sharply inverted T waves of Leads V_4 and V_5 were attributed to an outlying zone of ischemia rather than to left ventricular hypertrophy because of the normal QRS-T pattern in V_6. The standard leads showed marked left axis deviation, but were not diagnostic of infarction.

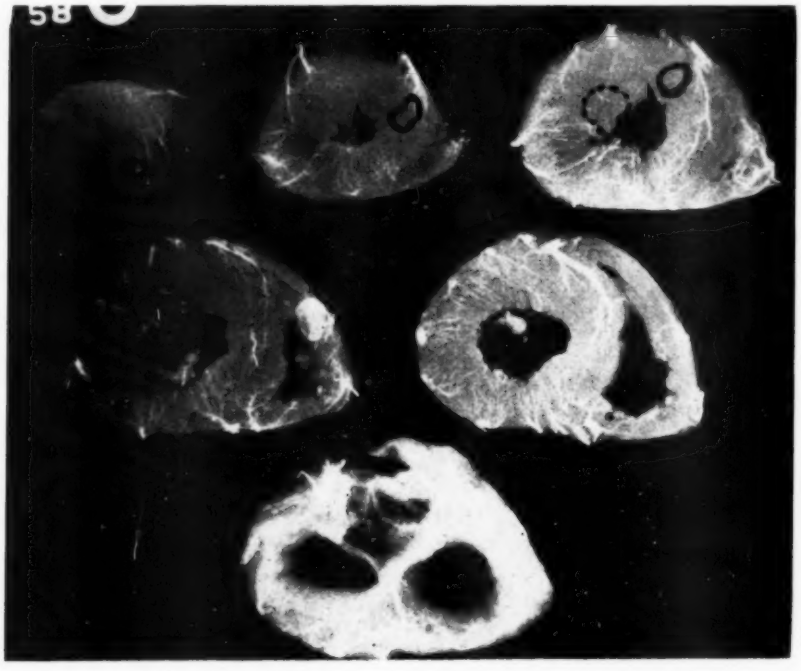

Fig. 7.—Roentgenogram of the heart of Case 4 injected with radiopaque mass and cut into transverse slices approximately 1 cm. thick. The position of the intramural anteroseptal infarct is indicated by the solid line and the location of the anterolateral infarct, by the broken line. In this and in all other illustrations of transversely sectioned hearts, the apical segment is located in the upper left-hand corner and the intervening segments are arranged in rows from left to right and then from above downward, ending with the basal segment, which includes the valular ring, in the lowermost row. Each slice is arranged so that the anterior surface of the ventricles is uppermost and the lateral wall of the left ventricle is on the reader's left. In the descriptions the apex is referred to as the first segment and the remainder are numbered consecutively toward the base.

Pathologic Findings.—The heart weighed 516 grams as a result of left ventricular hypertrophy. A relatively small infarct was found in the fourth and fifth segments, involving the subendocardial two-thirds of the anteroseptal wall of the left ventricle and the adjoining left side of the septum, as outlined in Fig. 9. There was microscopic evidence that the infarct had been present for two weeks or more. Thus, the QRS pattern in Leads V_1, V_2, and V_3 was well correlated with the location of the infarct at autopsy and the thickness of the wall involved; however, the impression that the infarct was very recent in origin and probably secondary to the precip'tous fall in blood pressure was incorrect. In the final analysis, there was uncertainty as to whether the RS-T pattern in Leads V_1 and V_2 was chiefly a residue of subendocardial injury or chiefly a result of Cedilanid.

CASE 6.—A man, 56 years of age, collapsed on the street and was admitted to the hospita in coma with a blood pressure of 240/140 and a rapid, totally irregular ventricular rhythm. Be

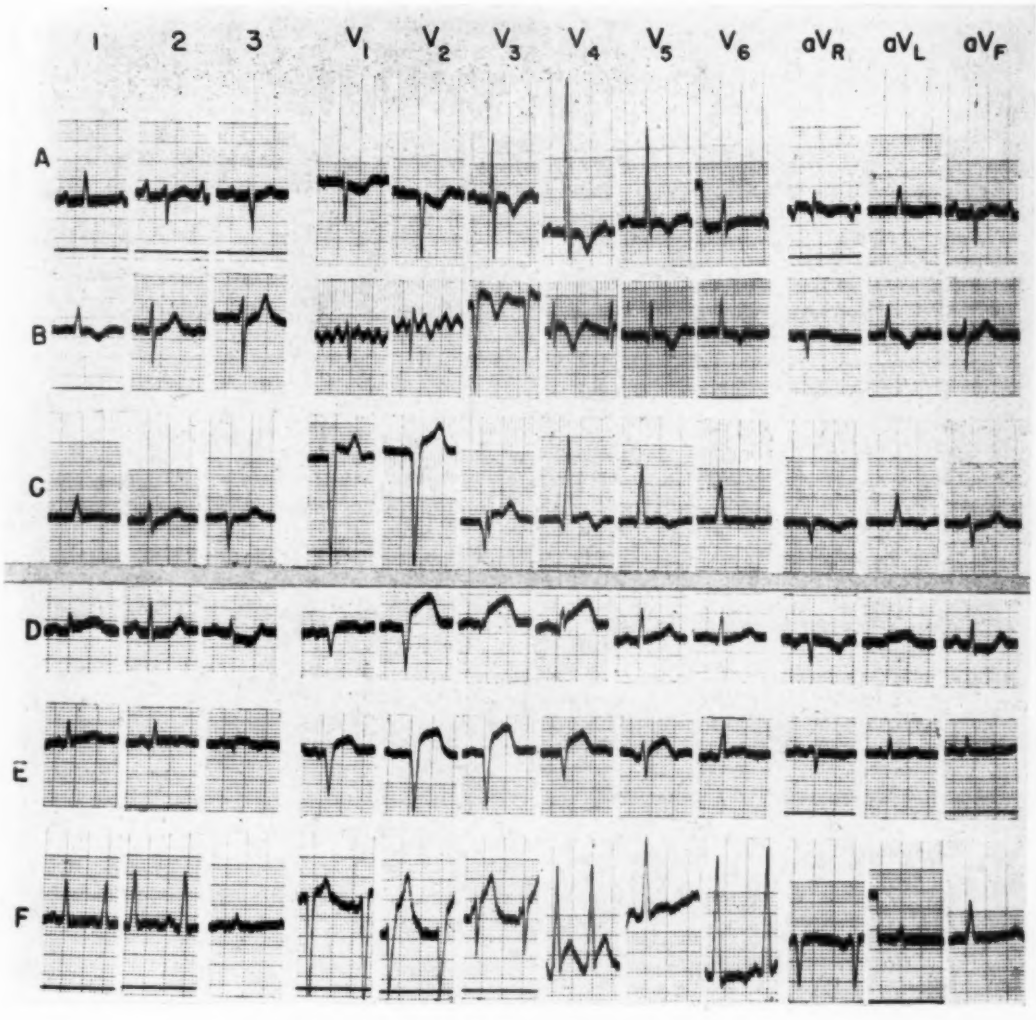

Fig. 8.—Recent anteroseptal infarction. *A*, Case 5; *B*, Case 6; *C*, Case 7; *D*, Case 8; *E*, Case 9; *F*, Case 10.

cause of repeated Jacksonian convulsions, a 500 c.c. phlebotomy was done, following which the blood pressure fell progressively to 85/70. No cardiac glycosides were given. The patient did not regain consciousness and died from the cerebral vascular accident forty hours after admission.

Electrocardiographic Findings.—An electrocardiogram obtained shortly after the blood pressure had fallen to shock levels and twenty-one hours before death is reproduced in Fig. 8,*B*. Although high voltage F waves due to an auricular circus movement overlay the QRS-T complex in Leads V_1 and V_2, a close study of the latter revealed a definite initial R wave in Lead V_1, measuring about 3.0 mm. in amplitude, and a deep Q and a late R in V_2. The T wave in Lead V_1 was completely obscured, but that in V_2 was clearly inverted. Lead V_3 exhibited a QS complex of central zonal type, an abnormally elevated RS-T junction, and cove-shaped inversion of the T wave. Lead V_4 showed a Q wave of 1.0 mm., an R wave of 7.0 mm., and an S wave of 3.0 mm. with elevated RS-T junction and cove-shaped inversion of the T wave representative of a marginal

zone. From the QRS changes, a diagnosis was made of a small transmural anteroseptal infarct situated nearer the apex than in Case 5, and from the RST-T pattern the infarct was considered recent in origin and accompanied by injury to the subepicardial layer. The standard leads showed left axis deviation with inversion of T_1, but were not diagnostic of infarction.

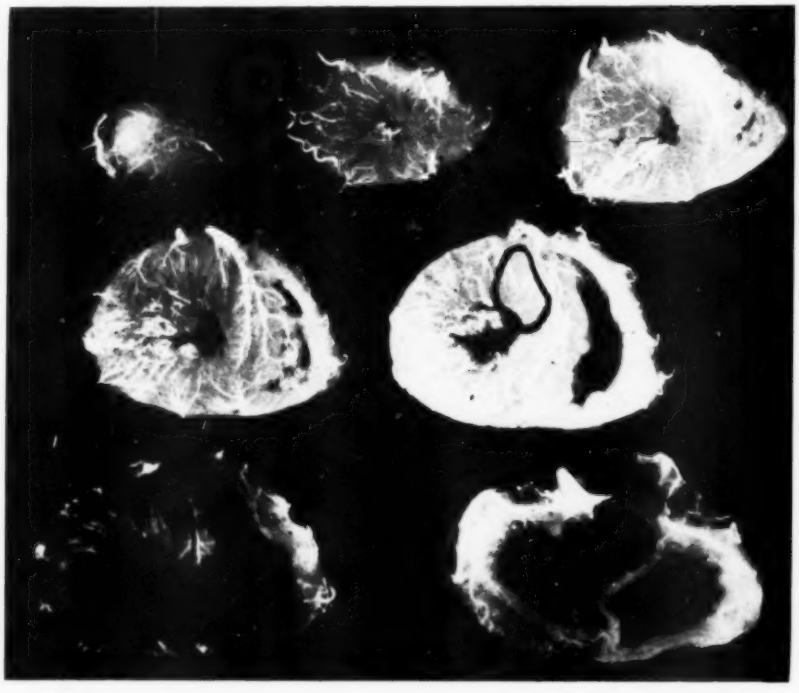

Fig. 9.—Roentgenogram of the heart of Case 5, showing high anteroseptal infarct outlined in black.

Pathologic Findings.—The heart weighed 501 grams because of left ventricular hypertrophy. An infarct was not seen grossly, but by means of multiple microscopic blocks was found to be present in the areas outlined in Fig. 10. The infarct was transmural in the fourth segment and involved the subendocardial one-half to three-fourths of the second and third segments. The age of the lesion was judged to be approximately twenty-four hours. Thus, the electrocardiographic and the autopsy findings were in close agreement both as to the location and the age of the infarct.

CASE 7.—A man, 58 years of age, gave a history of abrupt congestive failure nine months previously. He had had no thoracic pain until two days before admission when he was seized with severe constriction just to the right of the sternum. During the interim he was unable to pass urine, which was his chief complaint on admission. Physical examination revealed congestive failure complicated by circulatory collapse. Death occurred on the second hospital day.

Electrocardiographic Findings.—An electrocardiogram obtained on the first hospital day, after the administration of 1.2 mg. Cedilanid, is reproduced in Fig. 8,*C*. In Lead V_1 there was a distinct initial R wave 1.0 mm. in height, followed by a deep, broad S wave compatible with left ventricular hypertrophy. The deep QS complex in Lead V_2 and the deep, broad Q and late R in V_3 were diagnostic of anteroseptal infarction. Although the Q wave in Lead V_4 was only ten per cent of the amplitude of the succeeding R, the time interval of 0.04 second from its onset to its nadir indicated that it was abnormal and attributable to a marginal zone of subendocardial infarction. In Leads V_2 and V_3 the RS-T junction was abnormally elevated, but the contour

of the RS-T segment and T wave was not typical of recent infarction. On the other hand, the inverted T waves of Leads V_4 and V_5 were suggestive of recent infarction and were probably independent of Cedilanid because of the abnormally prolonged Q-T interval. The standard leads were not diagnostic of the anteroseptal infarct, which was clearly revealed by the precordial leads.

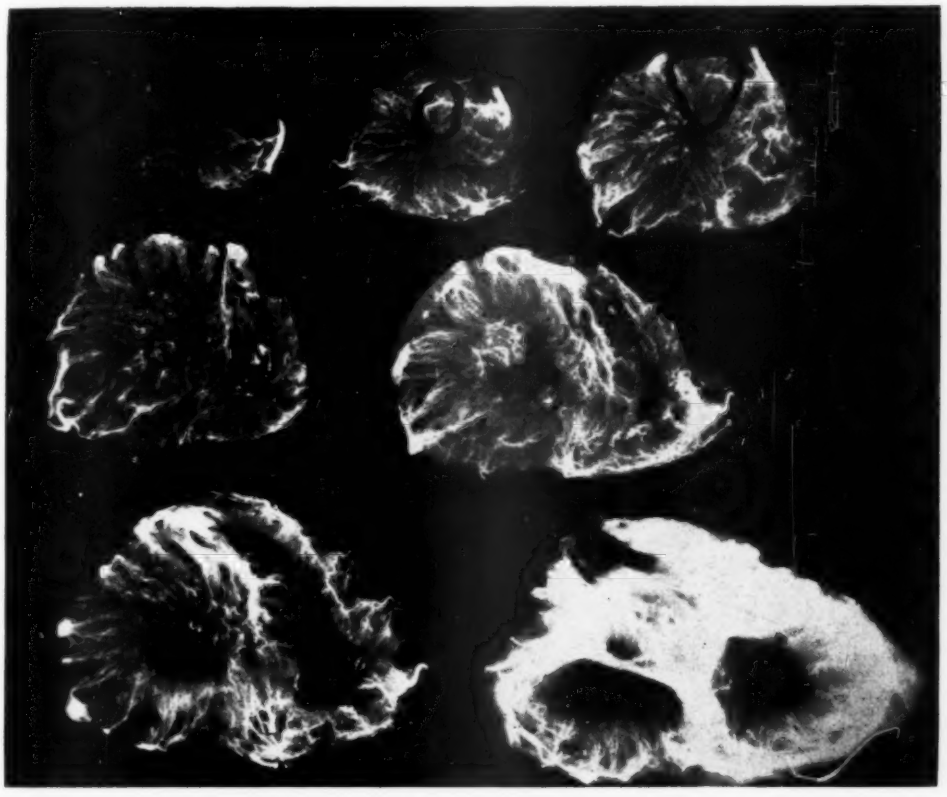

Fig. 10.—Roentgenogram of the heart of Case 6 with infarct outlined in black.

Pathologic Findings.—The heart weighed 543 grams because of left ventricular hypertrophy. A fusiform infarct was found in the apical 6.0 cm. of the anteroseptal wall of the left ventricle comparable in size and position to that of Case 2 (Fig. 4). The lateral wall was uninvolved. On microscopic examination, an old healed infarct involved the subendocardial one-third and a recent extension was found chiefly in the mid-zone of the myocardium, but projected in fingerlike fashion to the epicardium. The position of the infarct at autopsy and the thickness of the wall involved were thus in general agreement with the electrocardiographic predictions. The unusually tall R in Lead V_4 did not correspond with the fact that the infarct reached the anterior aspect of the apex. In view of the counterclockwise rotation, it may have been derived, in part, from the potential variations of the epicardial surface of the uninfarcted lateral wall.

CASE 8.—An obese diabetic woman, 43 years of age, was awakened at 4:00 A. M. by a severe retrosternal pain which radiated down both arms and was accompanied by repeated vomiting. The patient was hospitalized four hours later, but the pain continued despite frequent doses of morphine. No cardiac glycosides were given. Death occurred twelve hours after the onset of the present illness.

Electrocardiographic Findings.—An electrocardiogram obtained seven hours after the onset of the pain is reproduced in Fig. 8,*D*. A QS complex, which was slurred on its descending limb, was present in Leads V_1 and V_2; a splintered QRS of low voltage, which commenced with a Q wave, was found in V_3; and a Q wave of 1.5 mm., followed by a slurred R of 5.0 mm., was present in Lead V_4. The RS-T junction was markedly elevated in Leads V_2, V_3, and V_4, and the contour of the RS-T segment and T wave in these leads was typical of the stage of injury. The RS-T junction was very slightly elevated in Lead V_5, but the ventricular complex in Leads V_5 and V_6 was considered to be within normal limits. A diagnosis of very recent transmural anteroseptal infarct was thus made from the precordial leads. The standard leads in this case were indicative of anterior infarction, despite the fact that no signs were found in Leads V_5 and V_6. The reason for this was apparent from the unipolar limb leads. The pattern in aV_L corresponded closely to that in V_3, indicating that the potential variations of the infarcted anteroseptal wall of the left ventricle were referred to the left arm, rather than those of the uninfarcted lateral wall, as in the preceding cases. The pattern in aV_L was carried over into Lead I, accounting for the abnormal RS-T elevation. Judging from the QRS in aV_F, the potential variations of the posterior diaphragmatic surface of the left ventricle were referred to the left leg. The reciprocal RS-T depression in this lead was typical of that recorded over the intact wall opposite an acute infarct and was carried over into Lead III.

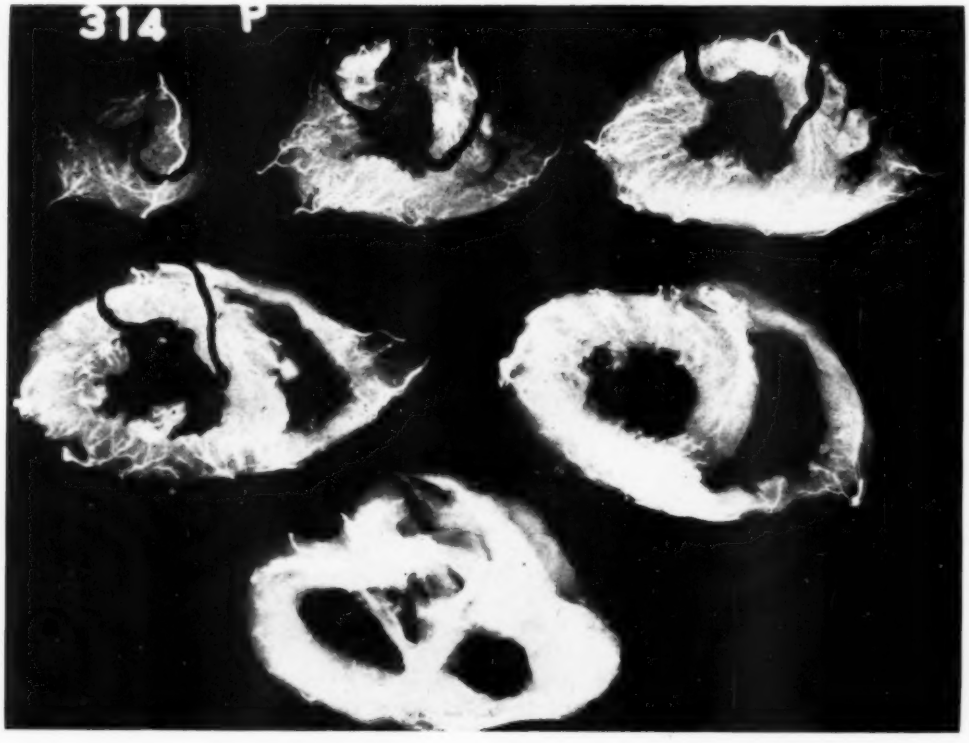

Fig. 11.—Roentgenogram of the heart of Case 8, showing rupture of the anterior wall in the second segment

Pathologic Findings.—The heart weighed 400 grams and exhibited a very recent transmural infarct involving the apical two-thirds of the anterior wall of the left ventricle and extending into the anterior two-thirds of the septum, as outlined in Fig. 11. Death was due to rupture of the anterior wall above the apex, as evident in the second segment of the roentgenogram. Since

Positions C_1 and C_2 were presumably over the uninfarcted right ventricle, the absence of the initial R from Leads V_1 and V_2 was correlated with the infarction of the septum and ascribed to obliteration of the positive potentials ordinarily referred to the right side of the precordium during septal activation. The RS-T displacement in Leads V_1 and V_2 was attributed to injury to the septum. The abnormal Q wave in Leads V_3 and V_4 was the result of the infarction of the anteroseptal wall of the left ventricle. In view of this apparently complete transmural necrosis, the presence of a rudimentary R in V_3 and a definite R in V_4 is noteworthy. The latter was most likely derived from the uninfarcted lateral wall. The involvement of the apex at autopsy was more extensive than had been anticipated from the presence of the distinct R in Lead V_4 and the practically normal QRS-T pattern in Lead V_5.

CASE 9.—A man 58 years of age, a chronic alcoholic, was admitted in an intoxicated state, complaining of acute retrosternal constriction and dyspnea. He gave a history of a similar attack two months previously which had lasted only one-half hour. No cardiac glycosides were given. Hospital course was uneventful until the sixth day when he suddenly died.

Electrocardiographic Findings.—An electrocardiogram obtained approximately forty-eight hours after the onset of the present illness is reproduced in Fig. 8,*E*. Leads V_1, V_2, and V_3 exhibited a QS, an abnormally elevated RS-T junction, and a monophasic upright T wave indicative of a recent transmural infarct involving the anteroseptal wall of the left ventricle and the adjacent septum. A definite but small initial R wave was present in Leads V_4 and V_5 along with an abnormally high RS-T take-off, suggesting a marginal zone of patchy infarction reaching the epicardium. The RS-T junction in the complex of Lead I reproduced in the illustration showed a pseudo elevation due to upward drifting of the string, but in other cycles of this lead the RS-T was isoelectric and the ventricular complex within normal limits. The small QR_3, slightly elevated $RS\text{-}T_3$, and inverted T_3 raised the question of posterior infarction; however, a study of the Goldberger leads showed a normal QRS pattern in Lead aV_F and indicated that Q_3 was derived from the initially positive potentials of the left arm and thus not due to posterior infarction.

Pathologic Findings.—The heart weighed 447 grams because of left ventricular hypertrophy. A recent transmural infarct involving the apical two-thirds of the anteroseptal aspect of the left ventricle and adjacent interventricular septum was found; the infarct was comparable in size and location to that in Case 8 (Fig. 11). The lateral and posterior walls of the left ventricle were not involved. Electrocardiographic and pathologic findings were in agreement both as to the location and age of the infarct.

CASE 10.—A man, 74 years of age, was admitted with extreme orthopnea and cyanosis. History was unobtainable. Examination revealed left ventricular hypertrophy, Type 3 pneumonia, and peripheral circulatory collapse. No cardiac glycosides were given prior to the taking of the electrocardiogram. The patient died of the pneumonia seven hours after admission.

Electrocardiographic Findings.—An electrocardiogram obtained shortly after admission is reproduced in Fig. 8,*F*. The initial deflection of the QRS was upright in all precordial leads. The amplitude and duration of the R wave in Lead V_6 were indicative of left ventricular hypertrophy. The striking feature was an abnormal RS-T elevation, which amounted to 7.0 mm. in Lead V_2, 4.5 mm. in V_3, and 3.0 mm. in V_4. The RS-T displacement in Leads V_2 and V_3 was much greater than that encountered in leads from the right precordium in the presence of uncomplicated left ventricular hypertrophy. Two possibilities were strongly considered: a pericarditis secondary to pneumonia and a recent anteroseptal infarct. The contour of the RS-T segment was typical of pericarditis, but the degree of elevation in Lead V_2 was greater than is generally produced by such a lesion. Furthermore, the limitation of the RS-T displacement to the first four precordial leads was against an inflammatory lesion, which because of its diffuse distribution would be expected to produce RS-T elevation in Leads V_5 and V_6 and in Lead aV_F as well. Thus, a diagnosis of recent anteroseptal infarct was favored, despite the atypical contour of the RS-T segment and the initial upright phase of the QRS. The absence of a Q wave was compatible with an infarct limited to the subepicardial layer or with an infarct distributed in patchy fashion through the wall. The standard leads showed low voltage of the T waves, but were not diagnostic of infarction.

Pathologic Findings.—The heart weighed 506 grams because of left ventricular hypertrophy. There was no evidence of pericarditis. An infarct was found by gross examination in an area corresponding to that of Case 2 (Fig. 4). Microscopic examination revealed that the infarct was patchy in distribution and was in part, old and in part, recent. The recent extension in the area of old infarction was probably a complication of the circulatory collapse consequent upon the pneumonia. The absence of Q waves may have been the result of the patchy character of the infarct. There was satisfactory correlation between the RS-T displacement in the electrocardiogram and the location of the recent infarct at autopsy.

CASE 11.—A man, 54 years of age, gave a history of anorexia and repeated vomiting of approximately two weeks' duration, right-sided pleural pain, scantily productive cough, and fever of two days' duration. There were physical and laboratory signs of right middle lobar pneumonia and uremia, the blood urea being 334 mg. per cent. At 2:00 A. M. following admission, he was awakened by extreme dyspnea without associated pain. Physical examination showed marked bilateral pulmonary edema. No cardiac glycosides were given. The patient died in circulatory collapse forty-four hours later.

Electrocardiographic Findings.—An electrocardiogram obtained eight hours after the attack is reproduced in Fig. 12,*A*. In Leads V_{3R} and V_1 there was a deep Q followed by an upstroke which extended 4.0 to 5.0 mm. above the isoelectric line. The RS-T segment sloped gradually downward to end in a sharply inverted T wave. Reciprocal, sharply peaked, upright T waves were present in Leads V_3, V_4, and aV_F, whence they were carried over into Leads II and III. The problem arose during life as to whether these electrocardiographic findings were the result of a recent high anteroseptal infarction, acute cor pulmonale secondary to the pneumonia, or hyperpotassemia associated with uremia. The deep Q, late R, and markedly elevated RS-T junction in Leads V_{3R} and V_1 pointed strongly toward high anteroseptal infarction and were not adequately explained by either of the other alternatives. Furthermore, the base of the T wave was too wide and the apex not sufficiently pointed to be characteristic of hyperpotassemia. The standard leads showed a prominent S pattern and were not diagnostic of infarction.

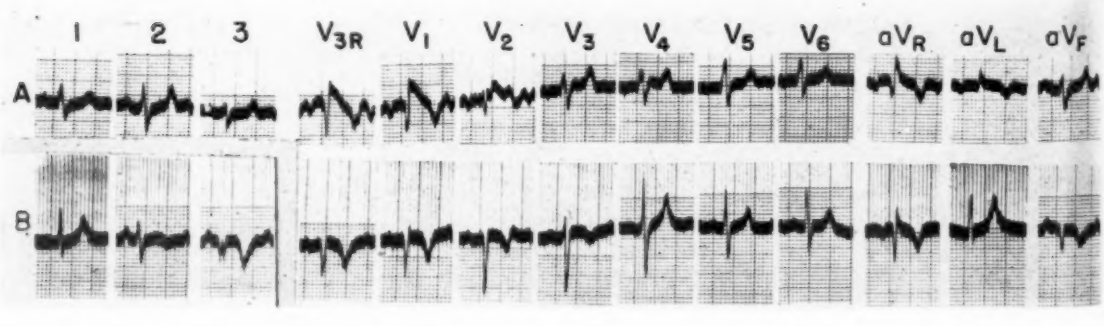

Fig. 12.—Recent anteroseptal infarction. *A*, Case 11; *B*, Case 12.

Pathologic Findings.—Both lungs were markedly edematous and a right middle lobar consolidation was present. There was no evidence of pulmonary embolism. The heart weighed 420 grams and exhibited slight left ventricular hypertrophy. The right ventricle was not hypertrophied nor appreciably dilated. An infarct was not seen grossly, but was found microscopically in the two basilar segments occupying the anteroseptal wall of the left ventricle, the anterior portion of the septum, and the adjacent margin of the right ventricle, as outlined in Fig. 13. The infarct was estimated to be of two days' duration. The poor injection of the anterolateral wall of the left ventricle was due to a technical error, since the left coronary artery was not occluded and multiple microscopic sections outside of the area outlined were negative. The recent infarction of the anterior part of the base of the septum and the immediately adjoining walls of the

right and left ventricles could adequately account for the absence of the initial R and the localized RS-T elevation in Leads V_{3R} and V_1.

CASE 12.—A man, 40 years of age, was well until Sept. 11, 1946, when he was suddenly seized with stabbing pain in the left axilla, aggravated by breathing and accompanied by dyspnea. He recovered completely and was well until October 5, when he was suddenly taken with a similar pain in the right axilla, leading to admission the next day. X-ray films of the lungs revealed a small area of consolidation in the right base. The heart was negative and the blood pressure 122/80. Hospital course was uneventful until 4:30 A. M. on October 12, when he was awakened by constrictive retrosternal pain and failed to rally, expiring thirteen hours later. No cardiac glycosides were given.

Fig. 13.—Roentgenogram of the heart of Case 11, showing recent high anteroseptal infarct outlined in black.

Electrocardiographic Findings.—An electrocardiogram obtained nine hours before death is reproduced in Fig. 12,*B*. Lead V_{3R} showed a QS deflection, a very slightly elevated RS-T junction, and a sharply inverted T wave; Lead V_1 displayed a deep Q, minute terminal R, and similar RST-T complex; Lead V_2 exhibited a minute initial R and a less deeply inverted T wave. In Lead aV_F a comparable T wave was found together with a QS complex, which exhibited a slight notch near the base of the descending limb. The question arose as to whether the pattern in Leads V_{3R}, V_1, V_2, and V_3 was due to pulmonary embolism or to anteroseptal infarction. The absence of a distinct initial R in Leads V_{3R} and V_1 pointed toward the latter, but a positive differentiation could not be made from a single electrocardiogram. It was most unfortunate that a tracing had not been obtained prior to the terminal episode. The pattern in Lead aV_F may have

been due to transmission of potential variations of the epicardial surface of the anteroseptal area to the left leg or may have been representative of extension of the infarct through the septum to the posterobasal portion of the left ventricle. The findings in Leads I and III were similar to those in Leads aV_L and aV_F, respectively, and gave no additional help in diagnosis.

Pathologic Findings.—A healed pulmonary infarct 1.5 cm. in diameter was found at the periphery of the left upper lobe. A slightly larger organizing infarct of about one week's duration was found near the periphery of the right middle lobe. No evidence of other pulmonary infarcts or terminal pulmonary embolism was uncovered. The heart weighed 350 grams and showed moderate right ventricular dilatation, but no hypertrophy. By means of multiple microscopic blocks, a very early patchy infarct was found distributed through the entire thickness of the basal three-fifths of the septum and extending through the adjoining anterior and posterior walls in the fourth and fifth segments, as outlined in Fig. 14. The infarct did not involve the outer

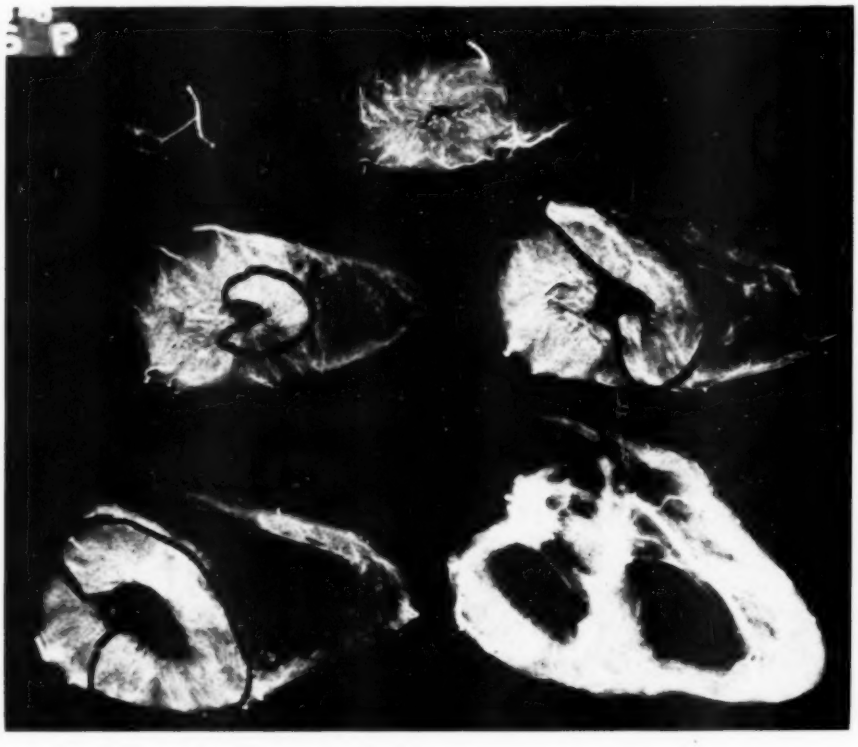

Fig. 14.—Roentgenogram of the heart of Case 12, showing position of infarct in black outline.

wall of the right ventricle. Hence, both the pulmonary embolism and acute anteroseptal infarction that had been considered during life were found at autopsy. Judging both from the reports of others and our own experience, the portion of the pulmonary arterial bed obliterated by emboli was too small to account for the striking changes in the QRS-T complex of Leads V_{3R}, V_1, and V_2. Thus, the findings in these leads were probably produced by the acute infarct of the interventricular septum and adjoining anteroseptal wall of the left ventricle. The findings in Lead aV_F were most likely the result of extension of the infarct into the posterobasal portion of the left ventricle.

CASE 13.—A woman, 95 years of age, died of pneumonia complicating a fractured femur. No history of myocardial infarction was obtained and no cardiac glycosides were given.

Electrocardiographic Findings.—An electrocardiogram taken three days before death is reproduced in Fig. 15,*A*. A QS complex was recorded in Leads V_1 and V_2. Since such a pattern may occur as a normal variant in V_1 and V_2 in conjunction with an upright initial deflection in leads farther to the left, the interpretation of the QS of V_1 and V_2 in this case depended upon the findings in the remaining leads. A Q wave approximately 0.03 second in duration and 25

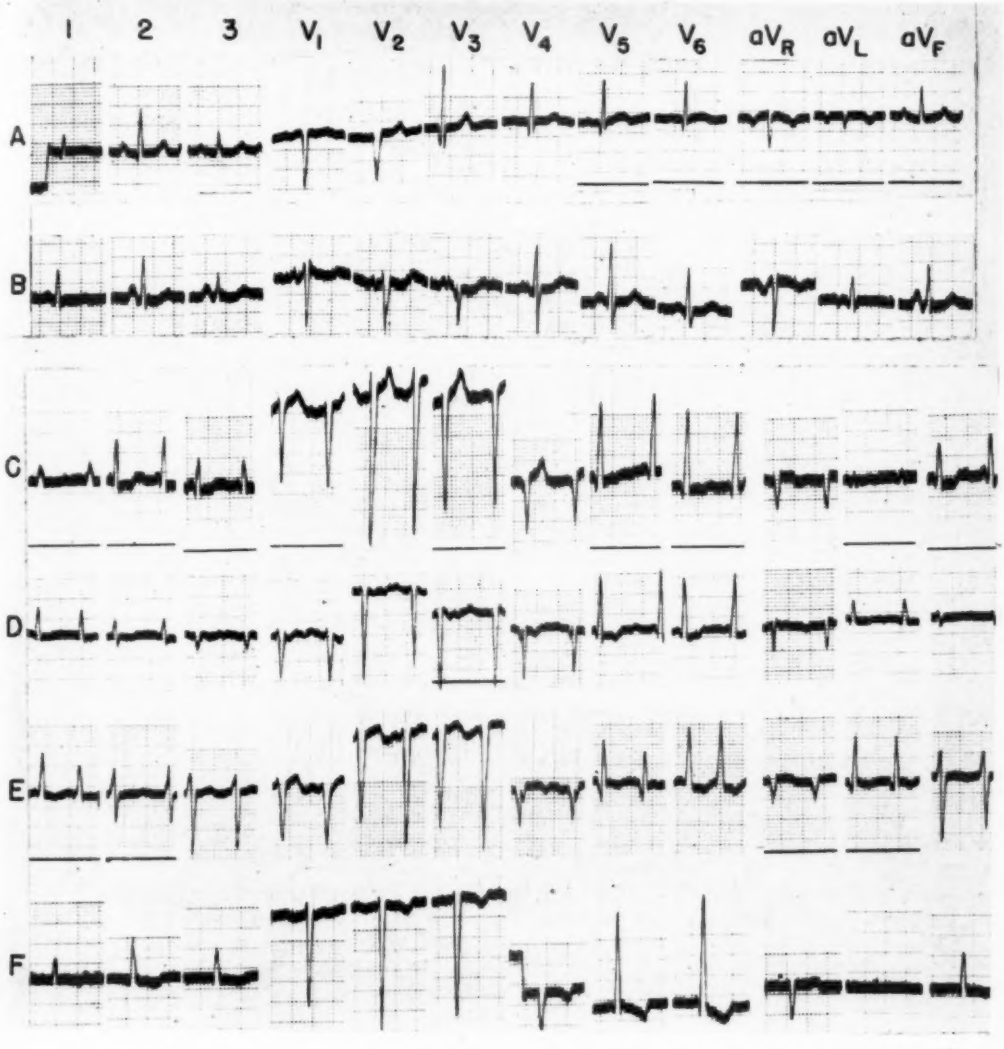

Fig. 15.—Old healed anteroseptal infarct. *A*, Case 13; *B*, Case 14; *C*, Case 15; *D*, Case 16; *E*, Case 17; *F*, Case 18.

per cent of the amplitude of the succeeding R wave was present in Leads V_3 and V_4. It is noteworthy that the Q wave in Leads V_3 and V_4 not only had a greater absolute duration and amplitude than that in V_5 and V_6, but also was larger in proportion to the R wave of the same leads. Since the Q waves in Leads V_3 and V_4 were thereby established as abnormal, the QS complexes in V_1 and V_2 were attributed to anteroseptal infarction. In view of the normal contour

of the RS-T segment and T wave, the infarct was considered to be old. The Q wave of 1.0 mm. and the R wave of 3.5 mm. in Lead I raised the question of old lateral infarct. Examination of the unipolar extremity leads showed that the heart was in vertical position. The inverted P wave in Lead aV_L suggested that the QS pattern in that lead may have been the result of transmission of the potential variations of the left ventricular cavity through the mitral orifice to the left arm, as discussed elsewhere.[29] The downward portion of the QRS in Lead aV_L was carried over as a Q wave into Lead I. Hence, no pathologic significance was attached to the findings in Lead I, and the standard leads were considered nondiagnostic of infarction.

Pathologic Findings.—The heart weighed 255 grams. A completely healed infarct was found in the subendocardial one-half of the anteroseptal wall. The infarct extended from the apex for a distance of 5.0 cm. toward the aorta and attained a maximal breadth of 3.0 cm. near the upper margin. The lateral and posterior walls were not involved. Thus, the position of the infarct was comparable to that of Case 2 (Fig. 4). An infarction limited to the subendocardial portion of the anteroseptal wall could adequately account for the abnormal Q waves in Leads V_3 and V_4, but does not ordinarily produce Q waves in V_5 and V_6. Since there was no evidence of lateral infarction to account for the Q waves in Leads V_5 and V_6, it is possible that there was sufficient rotation of the vertically placed heart to permit transmission of the potential variations of the anteroapical aspect of the left ventricle to the axilla. The infarct did not appear to extend sufficiently through the anteroseptal wall or into the septum to explain adequately the QS pattern in Leads V_1 and V_2.

CASE 14.—A man, 55 years of age, was admitted in uremic coma, secondary to prostatism. Although no history of cardiovascular disease could be obtained, a total of 1.6 mg. Cedilanid was administered during the first few hours because of the presence of cardiac enlargement and pulmonary edema. With the relief of the prostatic obstruction, the blood urea fell from an admission level of 360 mg. per cent to normal, but death from multiple renal abscesses occurred on the twenty-second hospital day.

Electrocardiographic Findings.—An electrocardiogram obtained twenty-two hours after admission is reproduced in Fig. 15,*B*. Lead V_1 exhibited a distinct R and R′ deflection, each 2.0 to 3.0 mm. in amplitude and separated by a deep S wave. The R′ was most likely derived from activation of the conus pulmonalis. In Lead V_2 the R and downstroke of the S were similar to those of V_1, but the R′ deflection was replaced by slurring on the upstroke of the S wave. In Lead V_3 there was an initial Q wave, ranging from 1.0 to 3.0 mm. in depth, followed by an upright deflection, which exhibited considerable respiratory variation. In some cycles, as in that illustrated, it merely rose to the isoelectric line to form a notch on the descending limb of the Q wave, whereas in others it extended above the isoelectric line for a distance of 1.0 to 4.0 mm. to form an R wave. The succeeding downward component was two or more times the amplitude of the upright deflection. Lead V_4 displayed an initial Q wave, ranging from 0.5 to 2.0 mm.; an R wave, averaging 12 mm.; and an S wave, averaging 8.0 mm. in amplitude. If all of the cycles in Lead V_3 were like that illustrated, a definite diagnosis of anteroseptal myocardial infarction could have been made from the electrocardiogram. In view of the marked respiratory variations in this lead, a presumptive diagnosis was all that was justified. The downward bowing of the RS-T segment was attributed to Cedilanid. There was no evidence in either the RS-T segment or T wave to suggest recent infarction. The standard leads were not diagnostic of infarction.

Pathologic Findings.—The heart weighed 460 grams and exhibited slight left ventricular hypertrophy. An old, completely healed infarct was found in the subendocardial one-third of the anteroseptal aspect of the apical three segments, as outlined in Fig. 16. The QRS pattern in Lead V_3 was presumably a manifestation of this subendocardial infarct. Nevertheless, when marked respiratory fluctuations in the contour of QRS are present, caution must be exercised in making diagnostic inferences from the electrocardiogram. This is illustrated by a case to be reported in detail in a future communication. The tracings in this case exhibited a prominent R and deep S wave in Leads V_1 and V_2 and an initial Q wave in V_4 ranging from 2.0 to 5.0 mm. in depth and followed by an upright deflection which varied from a notch on the descending limb of the Q wave to an R wave 10 mm. in amplitude. Autopsy in this case revealed left and right ventricular hypertrophy, but no evidence of infarction.

CASE 15.—A man, 72 years of age, gave a history of repeated episodes of cardiac failure during the preceding three years, but denied thoracic pain. He was admitted in congestive failure and was digitalized, but died of bronchopneumonia on the fifth hospital day.

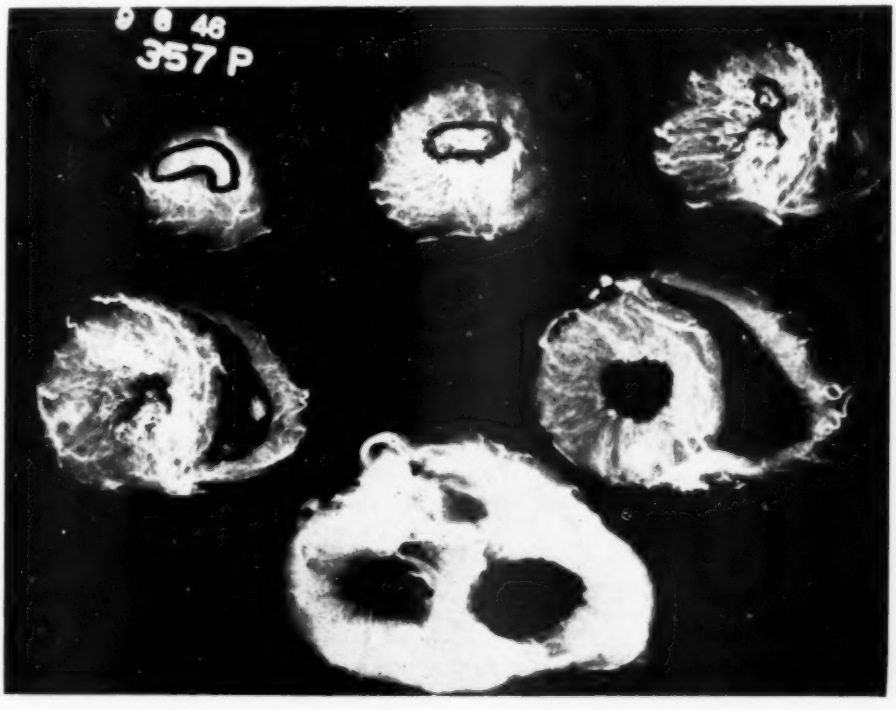

Fig. 16.—Roentgenogram of the injected heart of Case 14 with old healed subendocardial anteroseptal infarct outlined in black.

Electrocardiographic Findings.—An electrocardiogram obtained on the day of death is illustrated in Fig. 15,*C*. Auricular fibrillation was present. The initial deflection in Lead V_4 was consistently downward. A notched QS complex was present in V_4 in some cycles, while a small terminal R wave 1.0 to 2.0 mm. in amplitude was detectable in others. The Q wave in Lead V_4 was considered significant of anteroseptal infarction, in view of the distinct initial R wave in Leads V_1 and V_2 and the decreasing amplitude of the initial R wave in Lead V_3. The Q waves in Leads V_5, V_6, and aV_F were .02 second in duration and measured 10 to 15 per cent of the succeeding R and thus were compatible with left ventricular hypertrophy and were not sufficiently prolonged nor deep to be diagnostic of infarction. The RS-T depression in these leads was attributable to Cedilanid. The anteroseptal infarct was presumably old, since there were no characteristic T-wave changes of a recent lesion. The standard leads were abnormal, but were not diagnostic of infarction.

Pathologic Findings.—The heart weighed 654 grams and exhibited marked left ventricular hypertrophy and moderate secondary right ventricular hypertrophy. A patchy healed infarct was found localized in the subendocardial one-half of the anteroseptal wall of the left ventricle in the apical three segments, occupying the same position in the first two segments as that of Case 14 (Fig. 16) and involving the third segment in essentially the same manner as the second segment of Fig. 16. This infarct was probably responsible for the reduced R wave in Lead V_3 and the QS in V_4, but did not extend as far through the wall as would have been anticipated from

the findings in V_4. In view of the moderate clockwise rotation associated with the semivertical position, it is possible that the potential variations of the infarcted anteroapical wall might have been referred to the axilla and might have contributed to the Q waves in Leads V_5 and V_6. In the basilar one-half of the posterior wall of the left ventricle, there was a patchy fibrosis involving chiefly the subepicardial layer of muscle, but extending into the mid-zone, which was attributed to a separate infarct. When the electrocardiogram was reviewed in the light of the pathologic findings, it was concluded that the Q wave in Lead aV_F was too small and too brief in duration to justify the diagnosis of the posterior infarct found at autopsy.

CASE 16.—A man, 77 years of age, was admitted, moribund, in congestive heart failure complicated by bronchopneumonia and died thirty-four hours later. Past history was not obtainable.

Electrocardiographic Findings.—An electrocardiogram obtained after administration of 1.6 mg. Cedilanid is reproduced in Fig. 15,*D*. Auricular fibrillation was present. An initial R wave 1.0 to 2.0 mm. in height was recorded in Leads V_1 and V_2 and showed an abnormal decrease to 0.5 mm. in V_3. Lead V_4 displayed a Q wave followed by an upstroke which usually did not reach the isoelectric line, but in approximately one cycle of six, extended 1.0 mm. above the isoelectric line. Subsequent to this there was a deep downstroke, so that the complete complex in Lead V_4 consisted of a notched QS in most cycles and a triphasic QRS in occasional cycles. Since all cycles, including those with an R wave, displayed an abnormal Q pattern, a definite diagnosis of anteroseptal infarction was made from the electrocardiogram. The Q waves in Leads V_5 and V_6 were briefer in duration and smaller in proportion to the associated R waves than those of Case 15 and were not diagnostic of infarction. The changes in the RS-T segment and T wave were attributed to the Cedilanid. The standard leads were abnormal, but showed no characteristic signs of infarction.

Pathologic Findings.—The heart weighed 373 grams. Gross examination revealed an old, healed, well-vascularized anteroapical infarction almost identical in size and position to the anteroseptal portion of the infarct of Case 19 (Fig. 18). The infarct was confined to the subendocardial one-third at the apex, but extended through the subendocardial three-fourths of the anterior wall above the apex. Thus, there was close correspondence between the leads with QRS abnormalities and the position of the infarct at autopsy and rough correlation between the QRS pattern in these leads (V_3 and V_4) and the distribution of the infarct within the wall.

CASE 17.—A woman, 78 years of age, was admitted because of intestinal obstruction. She had had mild hypertension and moderate exertional dyspnea for a number of years, but gave no definite history of angina pectoris or myocardial infarction. Death occurred from peritonitis on the thirteenth hospital day.

Electrocardiographic Findings.—An electrocardiogram obtained on the second hospital day before cardiac glycosides were given is reproduced in Fig. 15,*E*. Auricular fibrillation was present. In Leads V_1 and V_2 there was an initial R wave 2.0 mm. in amplitude, and in Lead V_3 there was a definite though smaller R wave ranging from 0.5 to 1.0 mm. in height. In Lead V_4 there was a broad, deep Q wave, slurred on its descending limb and coarsely notched on its ascending limb. In a few cycles this notch extended slightly above the isoelectric line to form a late R wave. A prominent Q wave was also found in Lead V_5 which measured approximately .04 second in duration and ranged from 40 to 66 per cent of the amplitude of the succeeding R. A minute, insignificant Q wave was visible in Lead V_6. In view of the abnormal Q pattern in Leads V_4 and V_5, a diagnosis of infarction of the anteroseptal and anterolateral aspects of the apex was made. The RS-T junction was elevated in Lead V_4 and the terminal portion of the T wave was inverted. Since serial electrocardiograms were not obtained, the question as to whether this represented a recent organizing infarct or a fixed residue of an old infarct was left unanswered. The standard leads were abnormal, but were not diagnostic of infarction.

Pathologic Findings.—The heart weighed 334 grams. A completely healed, patchy transmural infarct was found, occupying the anteroseptal aspect of the apex and extending slightly into the subendocardial layer of the lateral aspect of the apex. The position was comparable to

that of Case 14 (Fig. 16), except that this infarct extended through the entire thickness of the anteroseptal wall in the two apical segments and extended subendocardially into the lateral aspect of the left ventricle in both of these segments. Thus, there was good correlation between the electrocardiographic and autopsy findings. Since there was an abnormal Q pattern in Lead V_5 and since the infarct at autopsy extended slightly into the lateral aspect of the ventricle, this was not, in the strict sense of the definition, an anteroseptal infarct. It has been included among cases of anteroseptal infarction for purposes of contrast.

CASE 18.—A man, 60 years of age, was admitted because of a sudden onset of aphasia, which proved to be the result of cerebral embolism secondary to auricular fibrillation. Past history was unobtainable. The patient died on the twenty-second hospital day of peritonitis from ruptured empyema of the gall bladder.

Electrocardiographic Findings.—An electrocardiogram obtained on the fourth hospital day after a total of 0.9 Gm. of digitalis is reproduced in Fig. 15, *F*. An R wave 2.0 to 3.0 mm. in amplitude was present in Leads V_1 and V_2 and a smaller but definite R wave was easily made out in V_3. In most of the cycles in Lead V_4 a QS complex was present, but in a few, a minute initial R wave 0.5 mm. in amplitude was detectable. In all cycles there was splintering of the apex of the downward deflection. An initial Q wave, which was relatively small in proportion to the succeeding R wave, was present in Leads V_5, V_6, and aV_F. The progressive diminution in the R wave as the electrode was moved from Position C_1 to C_4 was strongly suggestive of small anteroseptal infarction, localized near the apex, but was also compatible with right ventricular dilatation. The fact that the T waves were sharply inverted in Leads V_3 and V_4 and flattened in V_1 pointed toward the former, but positive diagnostic inferences were unwarranted because of rather typical digitalis effects in Lead V_6. Since further tracings failed to reveal the expected serial changes, a final ante-mortem interpretation was made of an old, healed, patchy anteroseptal infarct in the apical region. The standard leads were abnormal, but were not diagnostic of anteroseptal infarction.

Pathologic Findings.—The heart weighed 444 grams and showed moderate left ventricular hypertrophy. There was no evidence of right ventricular dilatation or pericarditis. An old, completely healed infarct was found in the anteroseptal wall of the apical two segments in a position similar to that of Case 14 (Fig. 16). A patchy transmural lesion was found in the apical segment, and the subendocardial one-third was involved in the second segment. In addition, the infarct in this case extended around the tip of the left ventricle to involve the posterior aspect of the apical two segments. Thus, the abnormal QRS pattern in Leads V_3 and V_4 was apparently a manifestation of the infarction of the anteroseptal portion of the apex found at autopsy. However, the somewhat larger infarct of the posterior wall of the apex was not clearly revealed by the electrocardiogram.

CASE 19.—A man, 47 years of age, began to have angina pectoris in the summer of 1943. On Oct. 8, 1943, he was awakened by severe protracted retrosternal oppression, and on October 22 he had a second similar attack. Since that time he had occasional attacks of angina pectoris, but no further episodes of protracted retrosternal pain. He dropped dead from exertion immediately after dinner on Nov. 3, 1944. No cardiac glycosides were given during the entire period of observation.

Electrocardiographic Findings.—Electrocardiograms selected from a series taken over a period of one year are reproduced in Fig. 17. In the first tracing of Sept. 3, 1943, taken before exercise, the initial phase of the QRS and the T wave were upright in all precordial leads and there was a progressive increase in the ratio of R to S wave as the electrode was moved from Position C_1 toward the left. In the second curve, taken on the same day immediately after exercise, there was no significant change in QRS, but the T wave became sharply inverted in Leads V_1, V_2, V_3, and V_4 and the RS-T junction dropped below the isoelectric line in Leads V_5 and V_6. This change was interpreted as evidence of ischemia of the anteroseptal wall of the left ventricle. The RS-T junction was depressed in Leads II and III; T_2 was diphasic; T_3 was inverted in the resting electrocardiogram and showed no significant change after exercise. The

tracing on October 8 was obtained eleven hours after the onset of the protracted retrosternal oppression. A small but distinct R wave was detectable in Lead V_1 similar to that present in previous tracings, but a QS complex was consistently present in Leads V_2 and V_3. The RS-T junction was slightly elevated in Leads V_1, V_2, and V_3 and the T wave was sharply inverted. These changes were indicative of a recent anteroseptal infarction. The QRS complex in Leads

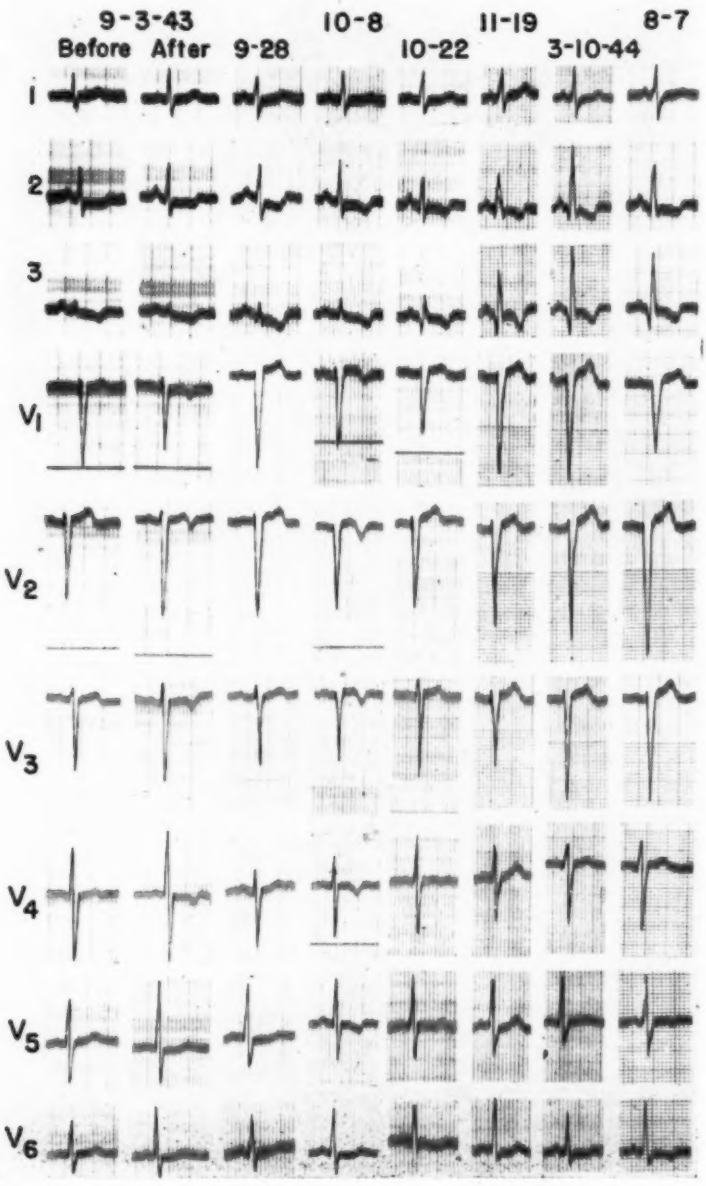

Fig. 17.—Serial electrocardiograms of Case 19, showing acute inversion of the T waves in the first precordial lead after exercise on September 3, anteroseptal infarction on October 8, and posterior infarction on October 22.

V_4, V_5, and V_6 showed no significant change, but the inversion of the T wave in Leads V_4 and V_5 was probably representative of an outlying zone of ischemia. By October 22 the QRS-T pattern in the precordial leads again resembled that in the initial tracing of September 3. It is noteworthy that a distinct R wave had reappeared in Leads V_2 and V_3 and, though abnormally small, was detectable in these leads in all subsequent tracings. Thereafter, the T wave in Leads V_1, V_2, and V_3 was consistently upright and fairly uniform in configuration, but that in Leads V_4, V_5, and V_6 varied in direction and amplitude. On October 22 a definite Q wave first appeared in Leads II and III and persisted in these leads, as well as in Lead aV_F, in the remainder of his tracings. The appearance of the Q wave in Leads II and III on October 22, together with the unusually rapid disappearance of the changes in Leads V_2 and V_3, was attributed to infarction of the posterior wall of the left ventricle.

Pathologic Findings.—The heart weighed 523 grams and exhibited left ventricular hypertrophy. Gross and microscopic examination revealed a well-vascularized infarct, involving the subendocardial one-half of the anteroseptal wall of the left ventricle, extending from the apex halfway toward the base. This infarct was continuous through the septum, with a larger healed subendocardial infarct involving the entire posterobasal portion of the left ventricle, as indicated in Fig. 18. The anteroseptal infarct found at autopsy confirmed the diagnosis made on

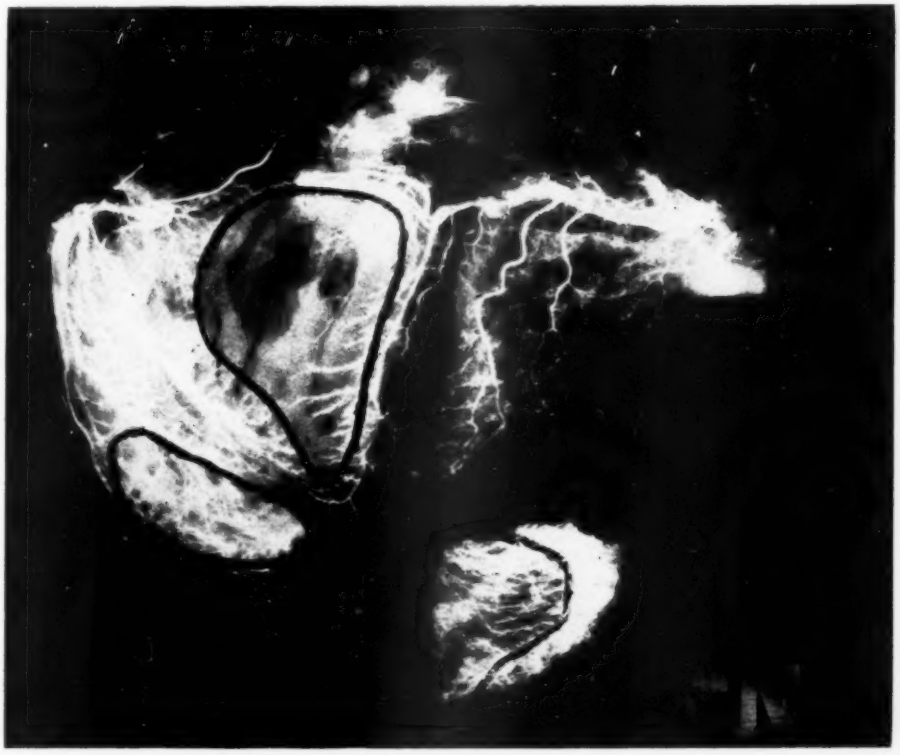

Fig. 18.—Roentgenogram of the injected heart of Case 19.

October 8, but extended farther toward the apex than had been postulated from the tracing. The posterior infarct was larger than had been anticipated from the tracing of October 22 and subsequent electrocardiograms. The records of Sept. 3, 1943, showed that ischemia of the anterior wall had preceded the infarction. Whether the RS-T depression and the T-wave inversion

in Leads II and III prior to October 22 were due to ischemia or to antecedent subendocardial infarction of the posterior wall remains in doubt.

CASE 20.—A man, 80 years of age, had an attack of prolonged retrosternal pain radiating to the back on Jan. 25, 1946, and was admitted three days later because of residual oppression. The patient was in good clinical condition on admission and remained so until 4.00 P.M. on January 29 when the retrosternal pain recurred, followed by shock and loss of consciousness. He failed to rally and died on February 2.

Electrocardiographic Findings.—An electrocardiogram taken on January 28, three days after the onset of the first attack of retrosternal pain and before the administration of cardiac glycosides, is reproduced in Fig. 19, together with a second tracing taken on January 30, twenty-two hours after the onset of the second attack of pain and after the administration of 0.8 mg. of Cedilanid. Leads V_1, V_2, and V_3 of the tracing of January 28 revealed a QS complex and a markedly elevated RS-T take-off typical of the central zonal pattern in the stage of injury. Lead V_4 displayed a small Q, a relatively tall R, and elevated RS-T junction, indicating a marginal zonal pattern. Since Leads V_5 and V_6 of the tracing showed no QRS abnormalities, a diagnosis was made of a recent infarct limited to the anteroseptal wall of the left ventricle and the adjacent anterior portion of the septum. The T pattern of V_4 was referred to the left arm and thus appeared in Lead I. It is noteworthy that Lead aV_F showed a fairly well developed initial R wave and a reciprocal RS-T depression, which carried over into Leads II and III. In the tracing of January 30 the appearance of a deep Q wave, a markedly reduced R wave, and an elevated RS-T junction in Leads V_4, V_5, and V_6 signified extension of the infarct into the lateral aspect of the apex, and the development of a W-shaped QRS in Lead aV_F indicated extension into the posterior aspect of the apex. The pattern in the standard leads of January 30 was also compatible with an anteroposterior infarct.

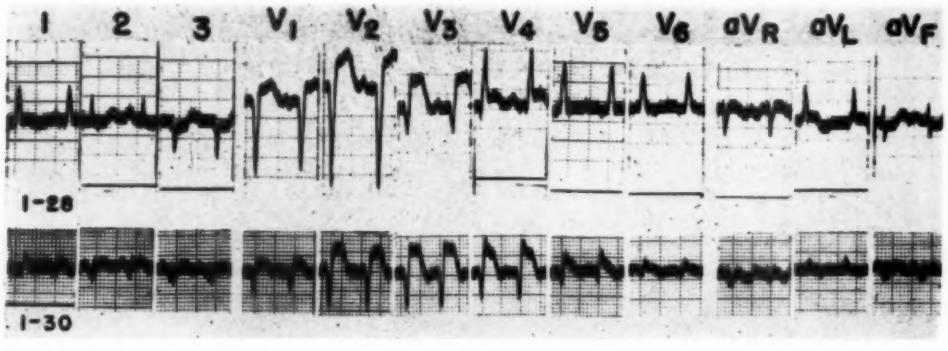

Fig. 19.—Electrocardiograms of Case 20, showing anteroseptal infarct on January 28 with extension to lateral and posterior aspects of apex on January 30.

Pathologic Findings.—The heart weighed 532 grams and exhibited left ventricular hypertrophy. There was a recent infarct, involving the left one-half of the septum and adjoining anteroseptal wall of the left ventricle, which had extended into the lateral and posterior walls of the apex, as outlined in Fig. 20. A terminal slitlike rupture had occurred at the junction of the anterior wall and septum in the third segment from the apex. The microscopic findings were in keeping with the electrocardiographic diagnosis of a recent anteroseptal infarct which had subsequently extended into the lateral and posterior walls of the apex.

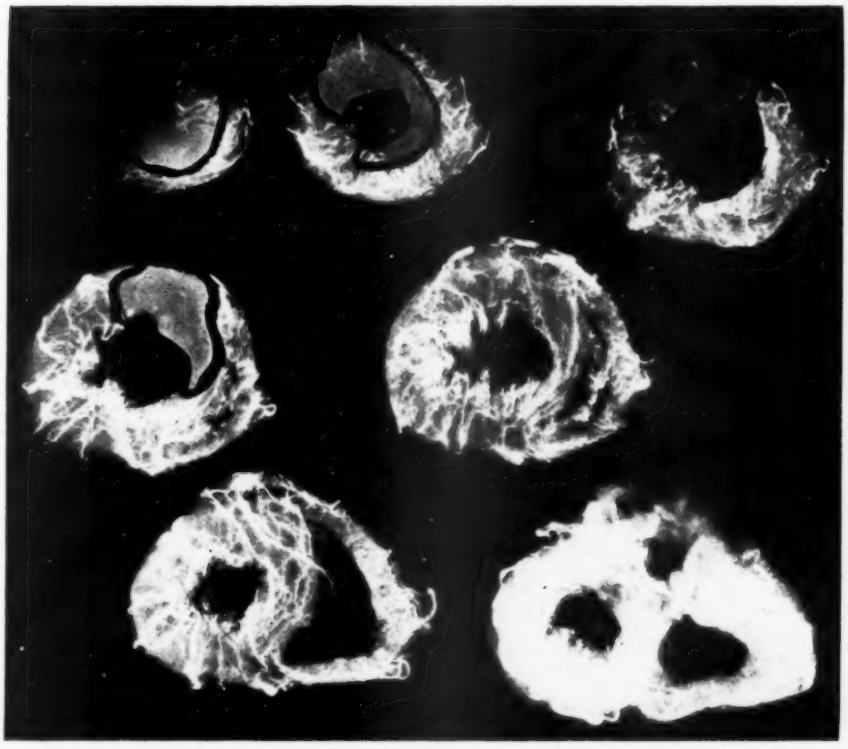

Fig. 20.—Roentgenogram of the injected heart of Case 20.

COMMENT

Electrocardiographic Signs of Anteroseptal Infarction.—The various patterns associated with anteroseptal infarction have been illustrated and discussed in the individual case reports and will be classified and summarized in this section. In general, the observations in this series of cases confirm and amplify the reports of Wilson and associates.[18,19,25]

Classical QRS Pattern in Anteroseptal Infarction.—This pattern is characterized by (1) presence of a normal initial R in Lead V_1 or in another lead from the right anterior chest wall; (2) replacement of the normal initial upright deflection in one or more of the next three leads (V_2, V_3, V_4) by a QS or an abnormal QR complex; and (3) absence of an abnormal Q wave from Leads V_5, V_6, and aV_L and the standard limb leads. The Q wave of a QR complex is considered abnormal when the time interval from its onset to nadir exceeds .02 second and when its amplitude is more than 25 per cent of the voltage of the succeeding R in every cycle. The entire lead should be examined to make sure that the abnormality in the initial phase of the QRS is present in every cycle, since marked respiratory fluctuations between an initial downward and an initial upward deflection may occasionally be observed in a lead at the transitional zone in the absence of myocardial infarction. A consistently abnormal

QR or QS deflection localized to Leads V_2, V_3, and/or V_4 is virtually diagnostic of anteroseptal infarction, particularly when Lead V_1 displays a normal RS complex consisting of a small, brief, initial upright deflection, averaging 2.0 to 3.0 mm. in amplitude and .01 to .02 second in duration, followed by a much larger and broader downward deflection. The presence of a QS deflection in Lead V_1 as well as in V_2 constitutes an indication for at least two additional leads from the right precordium, preferably V_{3R} and V_E. When an RS complex with normal initial upright deflection can be found in one or more of these leads, the QS in Leads V_1, and V_2 is, in all probability, the result of anteroseptal infarction. The qualification of the foregoing patterns, as practically diagnostic, rather than as pathognomonic, of anteroseptal infarction is necessitated for two reasons: (a) infarction localized to the lateral wall of the left ventricle may lead to abnormal Q waves in Leads V_2, V_3, and V_4 when there is sufficient counterclockwise rotation of the heart to cause transmission of the potential variations of the lateral wall to the precordium (this will be exemplified and discussed further in a subsequent manuscript on lateral infarction); (b) in uncomplicated right ventricular dilatation and hypertrophy,[30] a normal RS complex may be recorded in Lead V_1 and reduction or even disappearance of the initial R wave may occur in a transitional lead farther to the left. Since full consideration of the differentiation of the electrocardiographic findings in anteroseptal infarction from those in right ventricular dilatation and hypertrophy and from other patterns which may be confused, such as those of uncomplicated bundle branch block, left ventricular dilatation and hypertrophy, and pericarditis, would require a number of additional illustrations, it has been reserved as a subject for a separate communication.

Classical RST-T Pattern in Anteroseptal Infarction.—The findings in leads with an abnormal Q wave and/or abnormal reduction of the R wave depend upon the age of the infarction. Early in the stage of injury associated with a very recent infarction, the RS-T junction is elevated 2.0 to 8.0 mm. or more above the isoelectric line. The RS-T segment ascends to a peak in a straight line or a curved line with upward convexity (instead of the normal upward concavity) and the T wave returns precipitously to the isoelectric line, thereby completing a monophasic upright RST-T complex, as illustrated in Leads V_2, V_3, and V_4 of Cases 8 and 9. The RS-T displacement soon begins to recede and the terminal portion of the T wave starts to dip below the isoelectric line. As the RS-T junction approaches the isoelectric line, the T wave becomes more and more deeply inverted and takes on a characteristic cove plane contour. The RS-T segment begins at a point above or on the isoelectric line (but not actually depressed) and ascends in an arc with upward convexity to reach a level above the RS-T junction and then curves sharply downward to form an inverted V-shaped T wave with pointed apex and steep descending and ascending limbs. After reaching a maximal depth, the T wave gradually recedes. As it diminishes in depth, the gradient of the proximal and distal limbs becomes less and less steep, making the apex more and more rounded. The RS-T junction usually remains isoelectric or very slightly elevated and the RS-T segment generally retains its dome-shaped contour for a considerable time. Eventually

the T wave may become flat and finally may become upright and normal in contour. The foregoing classical evolution in the RST-T complex is illustrated in Lead V_2 of Case 2 (Fig. 3). However, stabilization may occur at any stage of the evolution. Thus, in some cases, the characteristic cove plane inversion of the T wave may remain permanently and in a few cases the upwardly displaced RS-T segment and monophasic upright T wave may persist indefinitely.

The combination of abnormal Q waves localized to Leads V_2, V_3, and V_4 with classical changes in the RST-T complex which has been described is pathognomonic of infarction and may be attributed to a localized anteroseptal infarct, provided there is no unusual degree of cardiac displacement or rotation. Isolated changes in the RS-T segment and T wave, resembling those just described, may occur in acute right ventricular dilatation and in pericarditis and consequently are not diagnostic of anteroseptal infarction. Their differentiation has been considered in the case discussions and will be elaborated upon in a subsequent communication.

In acute anteroseptal infarction, sharply inverted T waves may be recorded in Leads V_5 and V_6, whence they are transmitted to the left arm and registered in Leads aV_L and I. T waves of this description, when unaccompanied by an abnormal Q wave or abnormal reduction in the R wave, are a manifestation of an outlying ischemic zone and usually undergo a rather rapid evolution with return to normal or to a pattern more in keeping with underlying left ventricular hypertrophy.

Variants in the QRS Pattern in Leads V_1, V_2, V_3, and V_4.—The classical pattern which has just been described is not present in every case of anteroseptal infarction. It was found in seven of the twenty cases comprising this series (Cases 3, 6, 7, 15, 16, 17, and 19). In Case 19 the QS complexes localized to Leads V_2 and V_3 were very transient and initial R waves reappeared in these leads concomitantly with extension of the infarct into the posterior aspect of the left ventricle. In one additional case (Case 14) the QRS abnormalities were localized to Lead V_3 and were considered typical in some but not in all cycles due to modification from respiratory influences on cardiac position. The deviations from the classical QRS pattern in the first four precordial leads of the remaining cases could be classified into the following five categories:

1. Abnormal decrease in the amplitude of the initial R wave without complete disappearance of this deflection as the electrode was moved to the left from Position C_1 or C_2. This is exemplified by the electrocardiogram of Case 18, in which a 2.0 to 3.0 mm. initial R wave was found in Leads V_1, and V_2, a 1.0 mm. R wave in V_3, and an 0.5 mm. initial R wave in some cycles of V_4. Such a pattern may also occur in uncomplicated right ventricular dilatation and in right ventricular dilatation and hypertrophy. The differential diagnosis was considered in the discussion of Case 18.

2. A small but definite Q wave preceding an RS complex in Lead V_1 or in Leads V_1 and V_2. This is illustrated by Lead V_1 of Case 5, which displayed an 0.5 mm. Q wave followed by a 1.5 mm. R wave and a 10 mm. S wave. An initial Q wave preceding such an RS complex in Lead V_1 or in V_1 and V_2 is

abnormal and indicative of infarction of the interventricular septum, as will be further exemplified and discussed in a subsequent manuscript on that subject. A combination of this finding in Lead V_1 or in V_1 and V_2 with an abnormal QS or QR complex in Lead V_3 or in V_3 and V_4 is diagnostic of anteroseptal infarction.

3. The presence of a QS complex in Leads V_1 and V_2 or in V_1, V_2, and V_3. A QS complex was found in these leads in five cases of this series (Cases 2, 8, 9, 13, and 20) and was limited to Lead V_1 and to leads from the right anterior chest wall in three additional cases (Cases 1, 11, and 12). When an RS complex with normal initial R wave is not demonstrable in leads from the right side of the chest, a decision as to whether a QS complex in Leads V_1, and V_2 is due to anteroseptal infarction or to other causes, such as backward rotation of the apex,[21] will depend upon the QRS pattern in Leads V_3 and V_4 and the RST-T contour in the first four precordial leads. For example: in the antemortem interpretation of the electrocardiogram of Case 13, the QS of Leads V_1 and V_2 was attributed to anteroseptal infarction because of the presence of an abnormal QR complex in V_3 and V_4; in Case 9 the QS complexes of Leads V_1, V_2, and V_3 were evidently due to recent anteroseptal infarction because of the typical RST-T pattern in the same leads. Abnormal QS complexes in Leads V_1 and V_2 tend to occur as a result of extension of the infarct into the septum and are attributable to reduction or obliteration of the positive potentials ordinarily referred to the right side of the precordium during activation of the septum. When the infarct is confined to the basilar portion of the septum, as in Cases 11 and 12, the QS complexes and "coronary" T waves may be localized to Leads V_1 and V_{3R}. The QS complex limited to V_1 of Case 1 could be attributed to high anteroseptal infarction because of its observed development in serial tracings along with rather typical changes in the RS-T segment and T wave.

4. Right bundle branch block, characterized by the presence of a Q wave in place of the customary initial R wave in leads from the right side of the precordium. This may occur as a result of extension of an anterior infarct into the septum. Our cases of anterior septal infarction with right bundle branch block will be reported in a communication on septal infarction.

5. Absence of diagnostic abnormalities in the QRS complexes of the first four precordial leads. Serial changes in the T waves without significant QRS abnormalities in the first four precordial leads were observed in Cases 4 and 69 (to be reported later) during the acute stage of a small anteroseptal infarct, which subsequently proved to be intramural in location. Thus QRS abnormalities may be absent when the infarct is small and confined to the mid-zone of the myocardium (that is, when both the subendocardial and subepicardial layers are spared). Marked RS-T displacement without significant abnormalities in the initial phase of the QRS complex were observed in Case 10 in which autopsy revealed a considerably larger but patchily distributed infarct in the apical one-half of the anteroseptal wall. The absence of a Q wave in this case may have been due to the patchy character of the infarct.

Variants in the QRS Pattern in Leads V_5 and V_6.—Abnormal Q waves are characteristically absent from Leads V_5 and V_6 when the infarct is confined to the anteroseptal portion of the left ventricle. Their presence in these leads is usually the result of infarction of the anterolateral or lateral aspect of the apex, as exemplified by Cases 17 and 20. In the latter case, the extension of an anteroseptal infarct into the lateral wall was manifested by replacement of the normal initial R wave originally present in Leads V_5 and V_6 by an abnormal QR complex. When the heart is rotated clockwise on its longitudinal and anteroposterior axes, the potential variations of the epicardial surface of an infarct confined to the anteroseptal wall may be referred to the axilla and give rise to borderline or abnormal QR complexes in Leads V_5 and V_6, as in Cases 13 and 15. Under these circumstances, however, deeper, broader Q waves are recorded in Leads V_3 and V_4 than in V_5 and V_6. The distribution of the Q waves resulting from anteroseptal infarction differs significantly from the sites of predilection for the normal Q waves in left ventricular leads. The normal Q is deeper and broader in Lead V_6 than in V_5 and further diminishes or disappears in Lead V_4.

Variants in the QRS Pattern in the Standard Leads and in aV_L.—The well-known inadequacy of the standard limb leads in the detection of anteroseptal infarction was borne out by lack of diagnostic signs in these leads in eighteen of the twenty cases in this series. In the two remaining cases (Cases 8 and 20) there was RS-T elevation in Lead I and reciprocal depression in Lead III, which was strongly suggestive of recent anterior infarction. This was due to a cardiac position which favored transmission along a pathway from the C_3 or C_4 precordial position to the left arm in place of the more common pathway from axilla to left arm. This was evident from the resemblance of the pattern in Lead aV_L to that in V_3 of Case 8 and from the similarity of the findings in Lead aV_L to those of V_4 in the tracing of January 28 of Case 20. Thus, Leads aV_L and I may occasionally show diagnostic signs when the infarct is limited to the anteroseptal area.

Correlation of Electrocardiographic and Pathologic Findings.—This has been discussed in some detail in connection with each individual case report and will be summarized in this section. Wilson and associates[13-17] succeeded in demarcating the precise boundaries of experimental infarcts in animals through the use of multiple direct leads from the exposed epicardium. A similar degree of accuracy in the determination of the size and position of human myocardial infarcts cannot be achieved with multiple precordial leads, for obvious reasons: (1) A precordial lead is dominated by the potential variations of a much larger segment of myocardium than a direct lead and when situated at the border of the infarct will register an admixture of effects from the infarcted and outlying areas. (2) The anatomic relation of the heart to fixed points on the chest wall is subject to considerable variation among different individuals, because of differences in the size and position of the heart. This interjects an element of uncertainty in the prediction of the portion of the heart involved by a lesion responsible for a localized abnormality in the precordial leads. Furthermore,

Wilson and associates were able to demonstrate a close correspondence between the QRS pattern in a direct epicardial lead and the distribution of the infarct through the subjacent segment of myocardium. A similar degree of accuracy could not be attained with precordial leads unless the infarct is uniform in distribution throughout the entire segment of myocardium subtended by the electrode. In view of the foregoing considerations, it becomes of interest to correlate the findings in the precordial leads, which serve as an estimate of the surface area and location of the lesion and the proportion of the wall infarcted with the anatomic findings at autopsy.

Correlation Between the Leads Exhibiting Abnormal QRS Patterns and the Size and Position of the Infarct at Autopsy.—Extension of the infarct into the anterior portion of the interventricular septum was found at autopsy in thirteen cases of this series. An abnormal initial downward deflection was demonstrated in right ventricular Leads V_1 and V_2 or in V_1 and V_{3R} in seven of these cases (Cases 2, 5, 8, 9, 11, 12, and 20). For reasons already given, this initial downward deflection was ascribed to obliteration of the initial positive potentials ordinarily referred to the right precordium during septal activation and was therefore regarded as evidence of extension of the infarct into the septum. In the remaining six cases (Cases 3, 4, 7, 10, 16, and 19) Lead V_1 or V_1 and V_2 displayed an RS complex, which was not diagnostic of septal infarction. The septal involvement was patchy in all six cases and the initial R may have been derived either from preserved muscle in the septum or from the activation of the free wall of the normal right ventricle. Septal extension was not demonstrated pathologically in seven cases. A normal initial R wave was found in Leads V_1 and V_2 in four of these (Cases 14, 15, 17, and 18) and in V_1 in one case (Case 6). In the two remaining cases (Cases 1 and 13), where a QS complex was recorded in V_1 or in V_1 and V_2, it is possible that a septal extension was missed pathologically through failure to take microscopic sections through the septum. Thus, extension into the septum may be revealed by an abnormal initial downward deflection in right ventricular Leads V_1 and V_2 or may occur without diagnostic signs in these leads.

The infarction of the anteroseptal portion of the outer wall was classified, according to location, into the following three groups: (a) apical one-third to two-thirds, (b) middle one-third, and (c) basal one-third.

In fourteen cases, the infarct occupied the apical one-third to two-thirds of the anteroseptal wall. In one of these cases (Case 10), a diagnostic QRS pattern was not present in any precordial lead, perhaps because of the patchy character of the infarct. Of the remaining thirteen, Lead V_4 displayed an abnormal QS or QR in nine (Cases 3, 7, 8, 13, 15, 16, 17, 18, and 20) and an abnormal marginal zonal RS complex in one (Case 9). In Case 2, Lead V_4 displayed an ischemic zonal pattern in the early tracings and a marginal zonal pattern in the later tracings. The absence of diagnostic signs in Lead V_4 of the apical infarct found at autopsy in the two remaining cases (Cases 14 and 19) may have been due to a cardiac position which facilitated transmission of potential variations of the apex to a point medial to the mid-clavicular line. Lead

V_3 exhibited an abnormal QS or QR complex in ten of the fourteen cases and an abnormal RS of marginal zonal type in three (Cases 16, 17, and 18). An abnormal initial downward deflection was found in Lead V_2 in seven cases, but may have been referable to the associated involvement of the septum rather than the lesion in the outer wall. Leads V_5 and V_6 did not show a definitely abnormal initial downward deflection in any case where the infarct was confined to the anteroseptal wall. Borderline QR complexes were found in these leads in two cases where there was moderate clockwise rotation of the heart on its longitudinal and anteroposterior axes, and definitely abnormal QR complexes might result from more marked clockwise rotation. Thus, in general, there was good correlation between QRS abnormalities in Leads V_3, and V_4 and infarction of the apical one-third to two-thirds of the anteroseptal wall. However, accurate determinations of size and distinction between infarcts involving the apical one-third and the apical two-thirds of the anteroseptal wall could not be made from the findings in Leads V_3 and V_4.

The infarct was centered in the mid-portion of the anteroseptal wall in two cases. In one of these (Case 6) an abnormal QR pattern in V_2 was referable to the lesion in the outer wall, inasmuch as the septum was uninvolved. Lead V_4 of this case displayed a marginal zonal pattern, despite the fact that the infarct did not quite reach the apex. In the other case (Case 4) no abnormalities were found in the initial phase of the QRS, probably because of the small size and intramural location of the infarct, but serial changes in the T wave of Leads V_2 and V_3 corresponded, in general, with the position of the infarct.

The infarct was located in the basal one-third of the anteroseptal wall in four cases (Cases 1, 5, 11, and 12). Abnormal QRS patterns were limited to Leads V_1, V_2, and V_3 of Case 5, to V_1 and V_2 of Case 1, and to V_{3R}, V_1, and V_2 of Cases 11 and 12. Since infarction of the basal portion of the interventricular septum was demonstrated in three of these cases, the question was left unsettled as to whether the QRS abnormalities were due exclusively to the infarction of the septum or partly to the involvement of the adjacent anteroseptal wall. At any rate, there was good correlation between the leads showing QRS abnormalities and the basal location of the infarct.

Correlation Between QR Relationships in the Precordial Leads and the Distribution of the Infarct in the Underlying Myocardium.—Transmural infarction, extending from endocardium to epicardium, was demonstrated pathologically in thirteen of the cases. A QS complex was recorded in at least one lead of twelve of these cases. Notching or slurring of the QS deflection was present in the majority and could usually be correlated with preservation of islands of muscle in the infarcted area. The infarct was limited to the subendocardial one-half to two-thirds of the wall in six cases. A QS complex was present in at least one lead of all of these cases. In Case 19 the QS was a transient phenomenon during the acute stage and in Case 14 it exhibited respiratory metamorphosis to a QRS. The QS was notched in Cases 5, 15, and 16 and was accompanied by an intermittent late R in the latter two. In the remaining case

(Case 13) the QS was limited to Leads V_1 and V_2 and could not be satisfactorily correlated with the autopsy findings. Intramural infarcts limited to the mid-portion of the wall were found in Case 4 and in Case 69, to be reported later. These were manifested by serial changes in T waves without definite abnormalities in QRS. In general, there appeared to be a rough correlation between the QR relationships in the precordial leads and the distribution of the infarct between the endocardium and epicardium of the underlying wall; however, notched or slurred QS complexes, resembling those associated with transmural infarction, were found in cases where the infarct was limited to the subendocardial one-half of the wall.

Correlation Between the RST-T Pattern in the Precordial Leads and the Age of the Infarct at Autopsy.—The determination of the age of the infarct was greatly facilitated by serial tracings, as exemplified by Cases 1, 2, 3, 4, 19, and 20. A diagnosis of very recent infarction, made from marked upward RS-T displacement and monophasic upright T waves in Cases 8, 9, and 10, was verified at autopsy. However, cove plane inversion of the T waves in central zonal leads was demonstrated within a few hours after the development of the infarct in Cases 6, 11, and 12. An electrocardiogram in Case 2, taken nine hours after the onset of the attack and one hour before death, showed typical signs of a terminal posterior infarction, and autopsy revealed fresh occlusion of the right corornay artery, but no gross or microscopic evidence of infarction. These findings are in accord with the experience in animals, that electrocardiographic signs precede histologic evidence of infarction.[28] The single electrocardiogram in Case 5 revealed T-wave changes suggestive of recent subendocardial infarction, but autopsy disclosed an infarct which was considerably older than had been anticipated. The contour of the inverted T waves in the first electrocardiogram taken in Case 18 was suggestive of recent infarction, but the lack of significant change in subsequent tracings indicated a stabilized pattern from old infarction. Thus, a reliable estimate of age of the infarct cannot be made from a single electrocardiogram in the absence of other clinical data.

Diagnostic and Localizing Value of a Single Precordial Lead.—In a number of cases where a positive or presumptive diagnosis of anteroseptal infarction could be made from a study of multiple precordial leads, either no evidence or equivocal signs could be elicited from a single precordial lead, regardless of the position of the electrode. For example, the pattern in Lead V_4 was not diagnostic of infarction in Cases 1, 4, 5, 10, 11, 12, 14, and 19 and would have been equivocal in several other cases if leads on either side of the mid-clavicular line had not been available. The customary Lead IV, in which the electrode is applied over the apical impulse, probably would have given even less information, since the impulse was displaced beyond the mid-clavicular line near the C_5 precordial position in a number of the cases. The RS complex in Lead V_2 was not diagnostic of infarction in Cases 3, 4, 10, 11, 12, 14, 15, 16, 17, and 18 and the significance of the QS deflection recorded in this lead in several other cases would have remained in doubt without other leads for comparative purposes. Thus, the standard leads and a single precordial lead would have been

inadequate for diagnostic purposes in the majority of the cases of this series and would have been insufficient for localizing purposes in all cases.

SUMMARY

The findings in the Wilson precordial leads and in the standard and Goldberger limb leads have been correlated with the pathologic findings in 161 cases in which myocardial infarction was definitely established and accurately localized at autopsy. The cases have been classified in accordance with the anatomic location of the infarct into the following seven groups: anteroseptal, large anterolateral, anteroposterior, septal, posterior, posterolateral, and lateral. When classification into more than one category was possible, because of the large size or multiplicity of the infarct found at autopsy, the lesion of principal electrocardiographic interest became the determining factor.

This communication comprises a study of the electrocardiographic and pathologic findings in twenty cases of anteroseptal infarction. In the majority, the infarct was confined to a relatively narrow strip of the free anterior wall and the contiguous anterior portion of the interventricular septum. Serial electrocardiograms taken during the acute phase are presented in six cases and include a control tracing antedating the infarct in four cases, and one or more records after healing in four cases. Single electrocardiograms obtained during the stage of injury are presented in eight additional cases. The remaining six cases came under study after the infarct was completely healed.

In fourteen cases, the infarct involved the apical one-third to two-thirds of the anteroseptal wall of the left ventricle. The electrocardiogram in eight of these cases was characterized by a normal initial R wave in Lead V_1 and an abnormal QR or QS complex in one or more of the next three leads (V_2, V_3, and V_4). The Q wave of a QR complex was considered abnormal when the time interval from its onset to nadir exceeded .02 second and when its amplitude was more than 25 per cent of the voltage of the succeeding R. The electrocardiogram in five of the fourteen cases displayed a QS complex in Leads V_1 and V_2, as well as an abnormal initial downward deflection in Lead V_3 or V_3 and V_4. In four of these five cases, the QS complexes in Leads V_1 and V_2 were accompanied by abnormal elevation of the RS-T segment and could be correlated with extension of the infarct into the septum. The electrocardiogram of the last case in the group displayed marked RS-T displacement in Leads V_2, V_3, and V_4 without significant abnormalities in the initial phase of the QRS complex. The registration of an R wave in place of a Q wave in these leads could be correlated with the patchy distribution of the infarct through the anteroseptal wall.

In two cases, the infarct was centered in the middle one-third of the anteroseptal wall and did not reach either the apex or base. The tracing of one of these displayed a normal initial R wave in Lead V_1 and an abnormal QR or QS complex in the next three leads. Serial changes in the T waves of Leads V_2 and V_3 without significant QRS abnormalities were observed in the other case during the acute stage of an anteroseptal infarct, which subsequently proved to be small in size and intramural in location.

The infarct was located in the basal one-third of the anteroseptal wall in the four remaining cases and was manifested by an abnormal QR or QS pattern together with abnormal RS-T displacement confined to the first two or three precordial leads. Extension of the infarct into the basal one-third of the interventricular septum was demonstrated in three of these cases and may have been partly or wholly responsible for the QRS-T abnormalities in Leads V_1 and V_2.

Definitely abnormal Q waves were not found in Leads V_5 or V_6 in any case where the infarct was confined to the anteroseptal wall, but borderline QR complexes were recorded in these leads in two cases and were attributed to reference of the potential variations of the anteroseptal infarct toward the axilla as a result of clockwise rotation of the heart on its longitudinal and anteroposterior axes.

Diagnostic signs of anterior infarction were found in the standard limb leads in only two of the twenty cases. These three leads, together with a single precordial lead, would have been inadequate for diagnostic purposes in the majority of the cases in this series and would have been insufficient for localizing purposes in all cases. On the other hand, multiple precordial leads furnished adequate evidence in all cases for a positive or presumptive diagnosis of myocardial infarction and for a clinically satisfactory prediction of the position of the lesion.

The electrocardiograms were taken and mounted by Miss Josephine McDonald and were retouched by Miss Evelyn Erickson and Miss Geraldine Chesney.

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THE EFFECT OF INTRAVENOUS PROCAINE ON THE ELECTROCARDIOGRAM OF THE DOG

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During the past few years the intravenous administration of procaine has been found to be useful in the treatment of an increasingly greater variety of medical conditions. Investigators have reported its administration in attempting to control tinnitus aurium,[15] severe pruritus,[16] side effects of massive doses of neoarsphenamine,[23] allergic and drug reactions,[7] serum sickness,[4,21] reactions to penicillin,[12] pain associated with extensive burns,[14] postoperative pain,[1,19] dyspnea and asthma,[11] the severe pain of frostbite,[6] and for producing obstetrical analgesia.[3] Experimentally[2,8,9,13,17,20,22,24] and clinically[5,10,18] procaine has been shown to be partially effective in decreasing or controlling the activity of ectopic pacemakers in the heart.

The specific effects of this drug on the heart as manifested by electrocardiographic changes have not been previously reported; this is the purpose of this investigation.

METHODS

Eight dogs, anesthetized with pentobarbital sodium (25 mg. per kilogram of body weight), were used for this study. Use of the barbiturate was necessary to control the powerful convulsant action of procaine. After fifteen to thirty minutes were allowed for stabilization of the anesthetic level, 50 mg. per kilogram of procaine hydrochloride (made up as 50 mg. per cubic centimeter) was administered intravenously, the duration of injection varying between 15 and 120 seconds. Electrocardiograms (Lead II) were taken before, during, and at frequent intervals after the injections, and the records were analyzed for changes in heart rate, rhythm, and contour of the deflections.

RESULTS

The most striking changes were the tendency of the P-R and the QRS intervals to prolong, leading to the development of A-V and intraventricular block (Fig. 1). These findings appeared to vary with the rate of injection; that is, the more rapid the administration, the more pronounced the change. Nevertheless, the effects were present to some degree in all experiments. Further noted were: (1) a tendency for heart rate to increase or decrease, related generally to the speed

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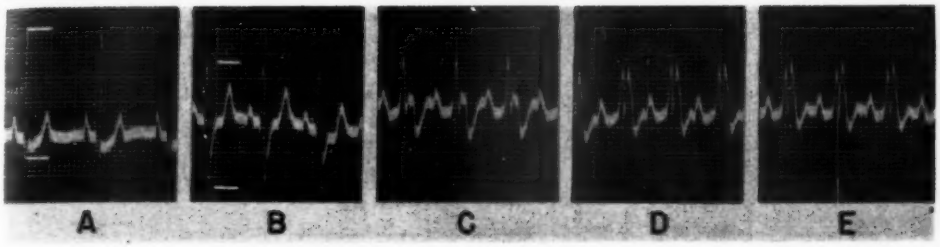

Fig. 1.—Effect of a rapid intravenous injection of procaine (300 mg. in fifteen seconds) on the P-R interval and QRS duration and contour (Lead II). The amplitude of QRS deflections is indicated by the short horizontal white markers in *A* and *B*. Note the development of first-degree A-V block and of intraventricular block. Record *A* is the control. *B*, *C*, *D*, and *E* were taken at fifteen-second intervals after the injection.

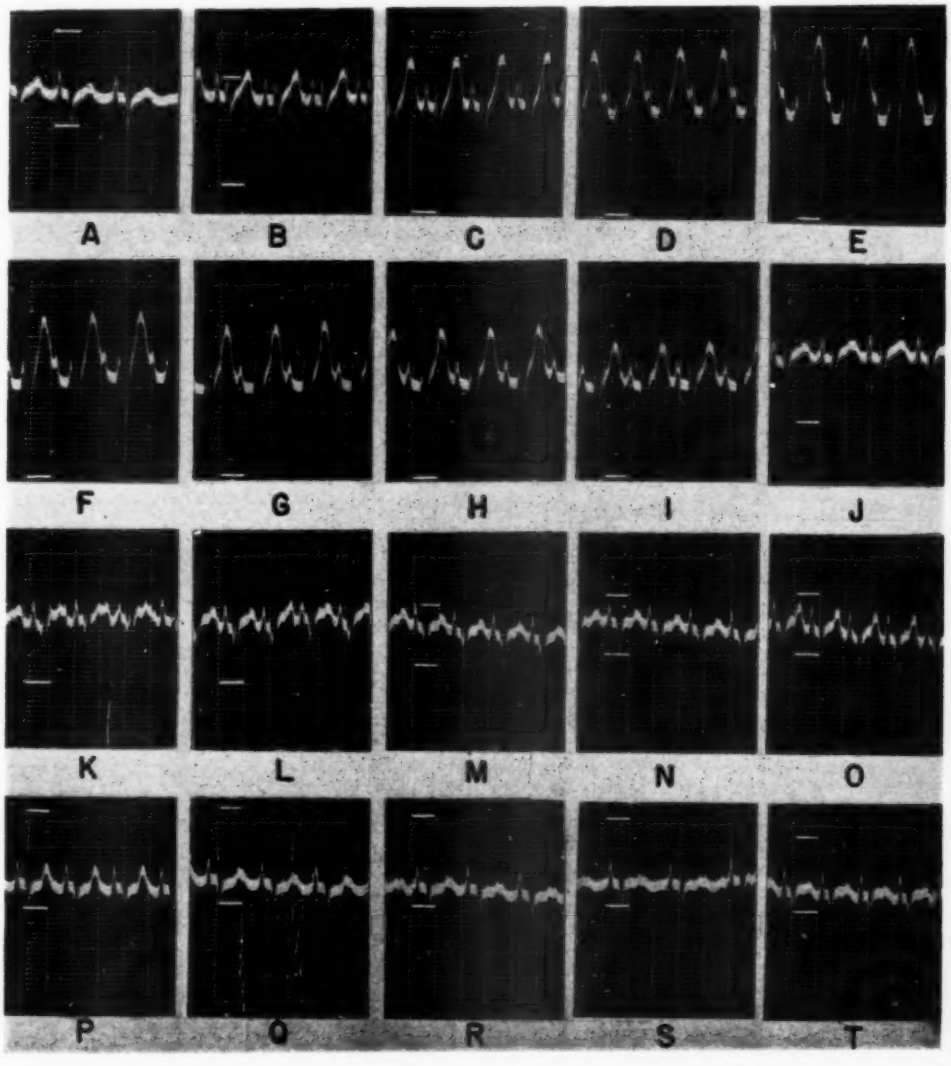

Fig. 2.—Progressive development of electrocardiographic changes (in Lead II) following injection of 50 mg. per kilogram of procaine intravenously in sixty seconds. Note increase in amplitude of P wave, prolongation of P-R interval, development of a deep S wave, and increase in duration of QRS; also, the early waxing and later waning of the T wave. *A* is the control. The time intervals following injection are as follows: *B*, fifteen seconds; *C*, thirty seconds; *D*, forty-five seconds; *E*, sixty seconds; *F*, one and one-half minutes; *G*, two and one-half minutes; *H*, three minutes; *I*, three and one-half minutes; *J*, six minutes; *K*, ten minutes; *L*, fifteen minutes; *M*, twenty minutes; *N*, twenty-five minutes; *O*, thirty minutes; *P*, thirty-five minutes; *Q*, forty minutes; *R*, forty-five minutes; *S*, fifty minutes; and *T*, fifty-five minutes. The horizontal white markers indicate amplitudes of the QRS complexes.

of injection; (2) an increase in the amplitude of the P wave; (3) a reduction in QRS amplitude in almost every instance, with the appearance of a deep S wave as the int aventricular block developed; (4) an increase in amplitude of the T wave independent of the change in heart rate.

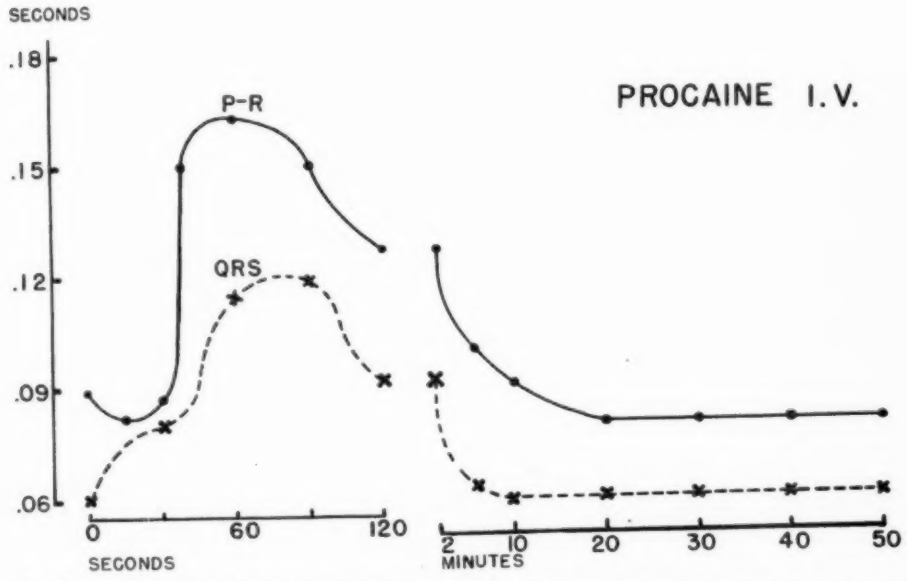

Fig. 3.—A graph illustrating the prolongation of P-R (solid line and dots) and QRS (broken line and crosses) following procaine injection. Time, abscissa: duration, ordinate. The values were obtained from the experiment shown in Fig. 2.

The progressive development of the electrocardiographic changes is illustrated in Fig. 2. Fig. 3 is a chart of the P-R and QRS changes which occurred in the preceding record. Fig. 4 shows the appearance of chaotic heart action following the very rapid injection of procaine intravenously.

DISCUSSION

From the observations noted it is apparent that procaine is a powerful depressant of the conduction system of the heart and progressively produces A-V and intraventricular block. It would appear, further, that there is an additional effect upon the myocardium, for the changes in QRS, S-T, and T configuration suggest some alteration in the depolarization and repolarization patterns.

Rapid administration of the drug intravenously is potentially capable of inducing a state of chaotic heart action as illustrated in one of the experiments. It is possible that this may have been the mechanism causing death in several of the clinical reports noted in the literature.

The changes in heart rate are probably the result of both cardiogenic and reflex factors. The slowing is most likely a reflection of the depressant action of the drug on the heart.

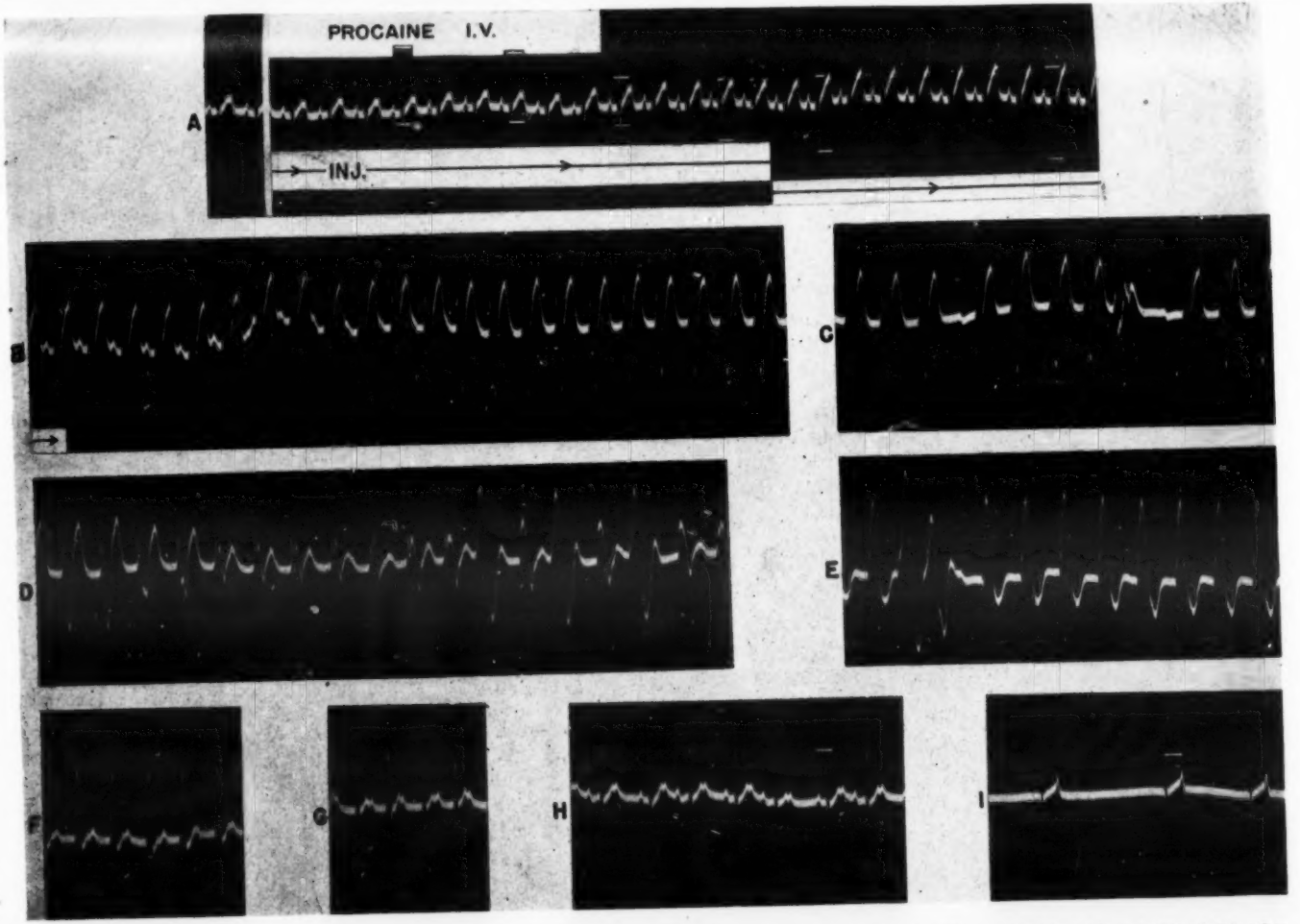

Fig. 4.—Chaotic heart action following the rapid injection of procaine intravenously (450 mg. in fifteen seconds); the period of injection is indicated by the horizontal arrow in *A* and *B*. *A*, control; *B* shows development of A-V and intraventricular block (note progressive merging of P wave with preceding T wave); *C*, *D*, and *E* show varying conduction disturbances in the ventricles and ectopic beats of ventricular origin (it is not possible to identify the P wave in these records); note notching of T waves in *F*, *G*, and *H*; P waves reappear in *H*; it is assumed that the tiny notch preceding the QRS complex in *I* is a P wave. The records were taken at the following intervals after injection: *B*, fifteen seconds; *C*, thirty seconds; *D*, one minute; *E*, two and one-half minutes; *F*, four minutes; *G*, five minutes; *H*, six and one-half minutes; and *I*, ten minutes. The horizontal white markers indicate amplitude of the QRS complexes.

It was felt that though the dosage level was high and the rate of administration rapid in these experiments, the potential hazards of the procaine could best be determined by evaluating the effects at their respective sublethal levels. Further, it should be borne in mind that hearts involved by inflammatory or degenerative lesions may tolerate only fractions of customary dosages of a given drug like procaine.

CONCLUSION

Intravenous administration of procaine in the pentobarbitalized dog caused significant changes in the electrocardiogram as evidenced by prolongation of the P-R and QRS intervals and by alteration of the configurations of P, QRS, S-T, and T deflections. In one instance it resulted in chaotic heart action with multiple ectopic pacemakers. Procaine is a powerful depressant of conduction.

We are indebted to Dr. L. N. Katz for his suggestions in the preparation of this report.

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HITHERTO UNDESCRIBED NEUROLOGICAL MANIFESTATIONS OF DIGITALIS TOXICITY

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THE involvement of the central nervous system in digitalis intoxication has been recognized and frequently reported in the literature since Withering's recognition of it in 1785.[1] Weiss[2] in 1932 stated that digitalis bodies acted directly on nervous structures, though the mechanism of action was not very well understood. Hueper and Ichniowski[3] and Dearing and associates[4] found extensive degenerative changes in the cortex, basal ganglia, cerebellum, pons, and spinal cord of animals made decidedly toxic with digitalis. These changes consisted of foci of vacuolated and disintegrating ganglion cells, necrosis, glial proliferation, and vascular changes.

The various neurological toxicities which have been reported are as follows: abnormal visual color sensations (especially yellow and green)[1,2]; blurred or dimmed vision[1,5-7,9-11]; diplopia[2,7,9,11]; temporary amblyopia[2,10,11]; scotomata[7-9,11]; flickering and glimmering of vision[2,10]; vertigo[2,5]; headache[2,5-7,10,11]; drowsiness[5,10]; malaise[10,11]; restlessness and irritability[2,5,9]; weakness and fatigue[2,5,6,8,11]; epileptiform convulsions[2,6,7,11]; hallucinations, illusions, and delusions[2,5,6,11]; confusion, disorientation, and delirium[2,7,9-11]; excitement or depression[2,5,7]; temporary loss of memory or aphasia[7,10,11]; and stupor and coma.[9] It should be noted that these toxic symptoms may occur regardless of the degree of toxicity and in the absence of any other manifestation of intoxication.

It is the purpose of this paper to present cases exhibiting peripheral and cranial nerve symptoms due to overdosage with digitalis products. These have not previously been reported, nor is there any reference in the literature wherein digitalis bodies are considered etiological factors in trigeminal or other neuralgias.

CASE REPORT

The following case was the first which drew our attention to these previously undescribed neurological aspects of digitalis toxicity.

M. V. was a 37-year-old white married woman with chronically active rheumatic heart disease involving both the mitral and aortic valves. She had presented the onset of diminished cardiac reserve at the age of 25 years. She had been digitalized several times for acute pulmonary edema, but the onset of rapid auricular fibrillation necessitated adjustment of digitalis dosage. The administration of a leaf product in doses of 0.2 Gm. three times daily for three days resulted

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in signs of toxicity manifested by anorexia, nausea, vomiting, and visual disturbances. Associated with these classical toxic symptoms was a severe facial pain characterized by a persistent aching of the teeth and lower jaw with superimposed lancinating pains along the distribution of the mandibular branch of the trigeminal nerve. Discontinuance of digitalis resulted in the cessation of all of these symptoms. Adjustment of digitalis dosage at repeated intervals over a three-year period was required for an uncontrolled rapid auricular fibrillation. On twelve separate occasions, similar attacks of facial pain associated with anorexia, nausea, vomiting, and green vision were noted. These symptoms occurred with the administration of digitalis leaf in doses of 0.1Gm. two or three times daily. Repeated dental examinations revealed no abnormalities.

This unusual case prompted us to review our experiences with toxic doses of various digitalis preparations to determine whether similar toxic manifestations were encountered. Studies in the evaluation of digitalis preparations and glycosides for the management of the ambulatory patient with congestive heart failure in progress for the past seven years lent themselves for this purpose. As part of this study, in order to determine the therapeutic range, the patient was given at periodic intervals an increasing dose of a digitalis preparation until minor signs and symptoms of toxicity supervened. The preparations studied included several lots of compressed tablets of Digitalis Purpurea, digitoxin, digoxin, lanatoside C, gitalin, urginin maritima, and urginin indica.

One hundred ninety episodes of toxicity were observed in ninety-six patients. Toxic episodes with different preparations in the same patient were counted as separate trials; but if more than one episode occurred with the same preparation, they were excluded. It is appreciated that patients may manifest the same toxic signs and symptoms to each of the preparations so that the incidence of any particular occurrence of an unusual symptom may be exaggerated. However, with a large group of subjects, the majority of whom had no more than two trials, this factor tends to be minimized.

Only the subjective manifestations of digitalis toxicity are considered here, since the true cardiac signs such as irregularities, arrhythmias, and various degrees of heart block may not have been present at the time the patient was examined in the clinic.

If each symptom is considered as a separate entity, a total of 600 occurrences of digitalis toxicity were observed in the 190 trials. These symptoms included anorexia, nausea, vomiting, diarrhea, abdominal pain, visual disturbances, weakness, nervousness, neuralgias and paresthesias, dizziness, headache, syncope, and tremors. It is of interest to note that approximately 41 per cent of the symptoms were neurological in nature. Neuralgias or related symptoms occurred thirteen times (2 per cent) in nine patients (9.4 per cent). The characteristics of these nine patients and the types of toxicity noted are presented in Table I.

DISCUSSION

The neurological manifestations of digitalis intoxication are more common than has been appreciated previously. Approximately 41 per cent of toxic symptoms involved some portion of the central or peripheral nervous systems. Gastrointestinal complaints are only slightly more common but it is our belief that the incidence of their occurrence and the importance of their recognition as indications of digitalis toxicity have been overemphasized.

TABLE I

NUMBER	PATIENT	SEX	AGE	CARDIAC DIAGNOSIS*	DIGITALIS PREPARATION	DOSAGE RESULTING IN TOXICITY	TOXIC MANIFESTATIONS	REMARKS
1	J. W.	F	34	(1) Rheumatic fever—inactive (2) Enlarged heart, mitral stenosis, mitral insufficiency, aortic insufficiency (3) Regular sinus rhythm	Urginin indica	3.0 mg. daily for two weeks	Nausea, vomiting, dizziness, headache, toothache, tremors of fingers, nervousness	Associated diagnosis of idiopathic epilepsy well controlled with phenobarbital and dilantin; these symptoms subsided two days after stopping digitalis preparation
					Urginin indica	3.0 mg. daily for five weeks	Anorexia, nausea, vomiting, dizziness, headache, visual disturbances, weakness, toothache, shooting pains posterior aspect of thigh	All symptoms subsided two days after medication discontinued
					Gitalin	1.25 mg. daily for six weeks	Nausea, vomiting, visual disturbances, toothache, pain of jaw bilaterally, pain posterior aspect of thigh	All symptoms subsided two days after medication discontinued
2	J. S.	F	46	(1) Rheumatic fever—inactive (2) Enlarged heart, mitral stenosis, mitral insufficiency (3) Auricular fibrillation	Digitalis leaf	0.2 and 0.3 Gm. alternate days for two weeks	Blurring of vision, bilateral lower jaw aching, intermittent for two weeks	Decreased digitalis dosage resulted in subsidence of symptoms within forty-eight hours
3	M. B.	F	58	(1) Hyperthyroidism and unknown (2) Enlarged heart (3) Auricular fibrillation	Digoxin	0.75 mg. twice daily for one week	Anorexia, nausea, vomiting, headache, fatigue, tingling of fingers, nervousness	Decreased dose of digoxin resulted in subsidence of symptoms within three days
4	Z. P.	M	51	(1) Unknown (rheumatic type) (2) Enlarged heart, mitral stenosis, mitral insufficiency (3) Auricular fibrillation	Digitoxin	0.3 mg. daily for four weeks	Anorexia, nausea, headache, weakness, fatigue, generalized muscle pains	Associated diganosis of essential hypertension

5	L. S.	M	52	(1) Unknown (2) Enlarged heart (3) Auricular fibrillation	Urginin indica	1.5 mg. daily for nine weeks	Anorexia, nausea, vomiting, dizziness, blurring of vision, shooting pains, and weakness of both upper extremities	
6	J. M.	M	41	(1) Rheumatic fever—inactive (2) Enlarged heart, mitral stenosis, mitral insufficiency, aortic stenosis, aortic insufficiency (3) Auricular fibrillation	Digitoxin	0.4 mg. daily for two weeks	Anorexia, epigastric pain, dizziness, blurring of vision, nervousness, severe burning pain of feet	
7	R. F.	F	48	(1) Rheumatic fever—inactive (2) Enlarged heart, mitral stenosis, mitral insufficiency, aortic insufficiency (3) Auricular fibrillation	Digitalis leaf	0.2 Gm. daily for two weeks	Anorexia, nausea, mild bilateral facial pain, generalized myalgias	
					Urginin maritima	1.5 mg. daily for four weeks	Anorexia, nausea, dizziness, headache, blurred vision, weakness, toothache, and soreness of entire jaw	All symptoms subsided in five days upon discontinuation of therapy
					Gitalin	0.75 mg. daily for two weeks	Epigastric distress, blurring of vision, sensitivity of teeth, shooting pains bilaterally lower one-third of face	Associated dental caries
8	N. C.	F	75	(1) Arteriosclerosis (2) Enlarged heart, myocardial fibrosis, coronary sclerosis (3) Auricular fibrillation	Digitalis leaf	0.1 and 0.2 Gm. alternate days for three weeks	Anorexia, headache, blurring of vision, shooting pains of lower extremities, nervousness	Complete cessation of all symptoms upon discontinuance of digitalis leaf
9	M. C.	F	51	(1) Rheumatic fever—inactive (2) Enlarged heart, mitral stenosis, mitral insufficiency, aortic insufficiency (3) Auricular fibrillation	Digitalis leaf	0.25 Gm. daily for three weeks	Nausea, dizziness, diarrhea, blurring of vision, numbness of lips and tongue, toothache	Associated idiopathic thrombocytopenic purpura

*According to Nomenclature and Criteria for Diagnosis of Diseases of the Heart, New York Heart Association, 1939.

The ten patients presented exhibited unusual neurological complaints. A careful survey of the literature failed to disclose any previous recording of such symptoms. It is of interest to note that these complaints occurred in approximately 9 per cent of patients manifesting digitalis toxicity. Apparently the gastrointestinal symptoms have been considered to be the classical manifestations of toxicity, and their occurrence overshadowed any other subjective complaint. It has been our experience that neurological disturbances not only may occur earlier than the classical gastrointestinal symptoms, but also may be the only indication of digitalis toxicity.

The neuralgic type of pain usually involved the lower one-third of the face simulating the syndrome of trigeminal neuralgia. The pain was characterized usually as a dull aching in the teeth or as a sharp and stabbing pain throughout the mandible or maxilla, or both. Other areas involved with typically neuralgic "shooting pains" were the upper extremity, lower lumbar area with posterior thigh radiation, and calf muscles. Parasthesias, such as tingling in the fingers and burning sensations in the feet, were also observed.

The type of digitalis preparation administered apparently played no role in the occurrence of these neuralgic complaints. We noted this toxic manifestation with digitalis leaf, digitoxin, digoxin, gitalin, urginin maritima, and urginin indica. It is very probable that the other cardiac glycosides when used in toxic doses will produce the same type of toxicity.

SUMMARY

1. Ten patients with unusual neurological manifestations of digitalis toxicity are presented.

2. Neuralgic type of symptoms were noted in approximately 9 per cent of patients receiving a toxic dose of a digitalis preparation.

3. The high incidence of neurological manifestations of toxicity has not previously been appreciated.

4. Neurological symptoms may be the earliest, the most severe, and the sole manifestations of digitalis intoxication.

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ACUTE PERICARDITIS OF BENIGN TYPE

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IN CLINICAL practice, the finding of acute pericarditis is usually regarded as evidence of the presence of some serious underlying disease such as rheumatic fever, myocardial infarction, uremia, tuberculosis, or pneumonia. There are, however, cases of pericarditis which pursue a relatively benign clinical course without evidence of any other disease. Recognition of these cases is highly desirable since their differentiation from other types of pericarditis and myocardial infarction is of great importance. Several descriptions of this benign form of pericarditis have appeared within recent years.[1,4,19] It is our impression that this condition is still not well known and that cases are being overlooked. The purpose of the present article is to describe seventeen additional examples of this condition, and particularly, to discuss the electrocardiographic findings which are of great value in the differential diagnosis (Table I).

CLINICAL MANIFESTATIONS AND LABORATORY FINDINGS

Based upon observations of our own cases and upon previous reports in the literature, the following is a general description of acute "non-specific" (idiopathic) pericarditis. Chest pain is the outstanding symptom. This most frequently occurs in the substernal or epigastric region but may be located also in the anterior chest, to either side of the midline, or in the shoulder. The pain may be quite severe, but is usually not as intense as that of myocardial infarction. It is commonly sharp and is characteristically aggravated by deep inspiration, turning of the body, coughing, sneezing, and, rarely, by swallowing. The discomfort may extend across the whole of the front of the chest, or may remain localized to the precordium. Radiation to the angle of the left scapula, to the neck, suprascapular region, or even down one or both arms may occur. The pain may be lancinating and intermittent, in contrast to that of myocardial infarction which is usually not sharp, and which is more often constantly present from inception until its gradual subsidence. Patients have variously described the discomfort as "sharp and cutting," "crushing," "pressing," or as a "feeling of indigestion." The duration is usually one to two days, but at times it recurs later during the course of the illness. Occasional twinges of pain may be experienced for some months. In rare instances, pain is insignificant.

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TABLE I. THE CLINICAL AND ELECTROCARDIOGRAPHIC FEATURES PRESENT IN SEVENTEEN CASES OF ACUTE PERICARDITIS OF BENIGN TYPE

CASE	AGE	ANTECEDENT RESP. INFECTION	FRICTION RUB	MAXIMUM WBC	MAXIMUM SED. RATE	MAXIMUM TEMP.	DURATION OF FEVER (DAYS)	PAIN	SIGNIFICANT ELECTROCARDIOGRAPHIC FINDINGS
1	40	0	+	10,000	20	101°F.	2	Severe precordial pain	S-T elevation I, II, III, and IV; T-wave inversion I, II, and IV
2	22	+	0	12,400	30	103°F.	3	Crushing substernal pain	S-T elevation I, II, III, and IV; T waves of increased amplitude; T-wave inversion I, II, III, and IV
3	46	+	+	10,000	0.8 to 1.2 mm. 48 to 72	100.8°F.	4	Pain in left shoulder aggravated by deep breathing, sneezing, and change of position; precordial tightness radiating to neck	S-T elevation II, III, and CR_4; T-wave inversion in I, II, III, and IV
4	25	+	0	10,200	—	100°F.	1	Griping, in epigastrium; shocking, stifling feeling	S-T elevation I, II, and CF_4; T-wave inversion in I, II, and III
5	22	0	+	11,200	—	101°F.	4	Sharp precordial pain	S-T elevation I and II; T-wave inversion in I, II, III, and IV
6	25	+	0	16,400	—	102.8°F.	5	Precordial ache radiating to left arm; feeling of indigestion	S-T elevation I, II, and IV; T-wave inversion in I, II, III, and IV
7	29	+	0	12,000	—	—	—	Muscular soreness followed by intermittent sharp precordial pain	S-T elevation I and II; T-wave inversion in I
8	32	0	+	12,000	42	101°F.	4	Severe indigestion; intermittent squeezing substernal pain	S-T elevation I and II; T-wave inversion in I, II, III, and CF_2

9	25	+	+	13,660	37	99.6°F.	1	Substernal pain and tightness radiating to left arm	S-T elevation I and II; T-wave isoelectric in I
10	18	+	0*	15,000	60	104°F.	7	Sudden severe precordial pain	ECG not taken at onset; T-wave inversion in I, II, III, and IV
11	39	—	0	8,000	16	100°F.	2	Excruciating precordial "scratching feeling"	S-T elevation I and IV; T-wave inversion in I, II, and III
12	34	0	0*	9,200	—	—	—	Sharp precordial pain	S-T elevation II and III; isoelectric T_1, diphasic T_2 and T_3
13	24	+	+	9,500	—	100.4°F.	3	Sharp substernal pain radiating to left shoulder	S-T elevation I and II
14	25	+	+*	13,900	72	102.8°F.	6	Precordial cramp with radiation to neck and left arm	S-T elevation I and II; T-wave inversion I, II, and IV
15	25	0	+	8,500	48	100.2°F.	3	Sharp precordial pain aggravated by inspiration, coughing, and turning	S-T elevation I, II, and III; T-wave inversion I, II, and IV
16	20	+	0	Normal	34			Intermittent pain over left upper chest	T-wave inversion in I, II, III, and IV
17	26	+	0	Normal	29	100°F.	2	Dull precordial pain and numbness of left arm	S-T elevation II and III; T-wave inversion I, II, and III; notched T in CF_4
3 (Second admission)	46	+	0		66	100°F.	3	Aching beneath left shoulder	T-wave inversion I and IV

*Pericardial effusion.

Dyspnea may be present as a result of the splinting of the chest. Syncope at the onset of pain or a drop in blood pressure to shock levels may occur, but such occurrence is rare.

A pericardial friction rub is frequently present, although not always detected. Repeated examination with the patient leaning forward in forced expiration, as well as in the recumbent and lateral positions, may be necessary for its demonstration. The rub usually disappears within twelve to twenty-four hours. Pericardial effusion occurs in some instances, and some observers feel that the heart may undergo actual dilatation.[1,2] The frequency of pericardial effusion is emphasized by a recent report of eight cases from a United States Army hospital[3] which may have been instances of this type of infection.

Fever usually occurs at the time of onset of pain and is usually mild, varying from 101° to 102°F. and lasting only a few days. It may reach 104°F. and persist as long as one week. Profuse perspiration is not uncommon. Most of the patients feel remarkably well after the first few days. Following recovery, there are no symptoms to suggest angina pectoris and none of the stigmata of rheumatic fever or rheumatic heart disease are present.

Recurrence of pericarditis is occasionally observed, and some authors[1] have suggested that this type of infection may at times be a factor in the etiology of constrictive pericarditis. Other serous membranes may be involved, and a history of previous pleurisy or the presence of an associated pleurisy is not infrequent.[4] Cases have been noted postoperatively, apparently unrelated to respiratory infection or pulmonary embolism.

Leucocytosis of a mild degree is common, although the leucocyte count is at times normal. The sedimentation rate is almost invariably elevated, but returns to normal in one to two weeks.

There is no specific treatment. The disease is self-limited, and the clinical features are frequently so brief that it would be most difficult to evaluate therapy. Sulfonamides and penicillin have had no apparent effect on the course of the disease.

ELECTROCARDIOGRAPHIC FINDINGS

The manifestations of pericarditis in the electrocardiogram have been demonstrated to be due to subepicardial myocarditis.[5-8] In the acute stage, the S-T segments become elevated in one or more leads. The elevation may occur in all leads or may be confined to Leads I and II, or Leads II and III, with or without elevation of the S-T segments in the precordial leads (Fig. 1). In rare instances, the S-T elevation may be confined to Lead I. The elevation may vary from 0.5 to 2.0 millimeters. In order to evaluate small amounts of elevation, it is necessary to have serial tracings, since it is not uncommon to find an elevation of 0.5 to 1.0 mm. in the tracings of normal individuals.[9,10] The S-T segments are concave, in contrast to the convex or cove plane segments so often seen in myocardial infarction. After one or two days, the S-T segments become horizontal or rectilinear, though still elevated, and the T waves become lower in amplitude (Fig. 2). There are never the reciprocal changes of the S-T segments such as occur in myocardial infarction. In pericarditis, if S-T changes are present, they are always in the

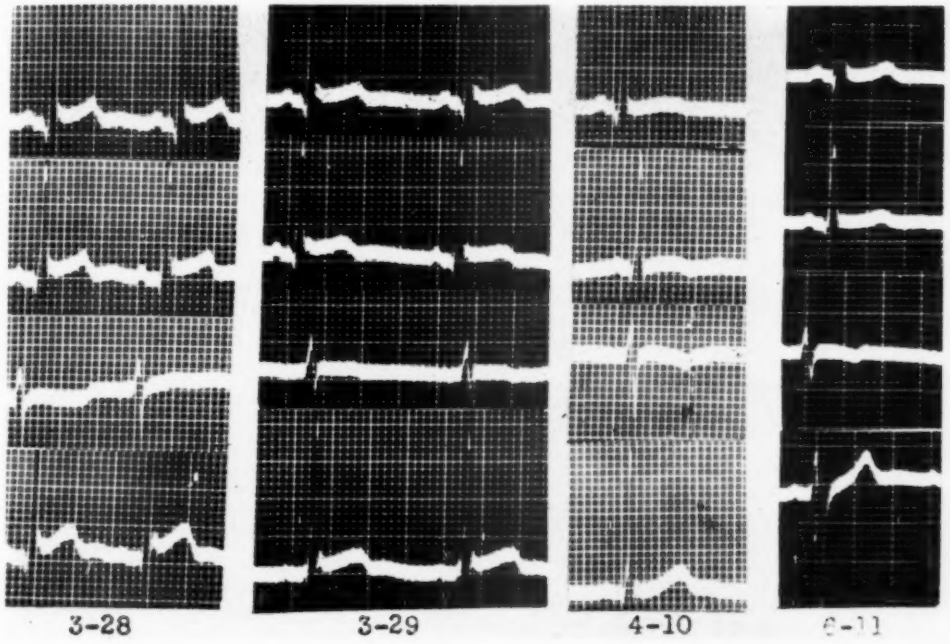

Fig. 1.—Case 7. The S-T segments are elevated on March 28. On April 10 T_1 and T_2 are beginning to invert. Note that there is no change in the normal Q_1 through the series of tracings. There is no reciprocal depression of S-T_3 as might be expected if this were myocardial infarction.

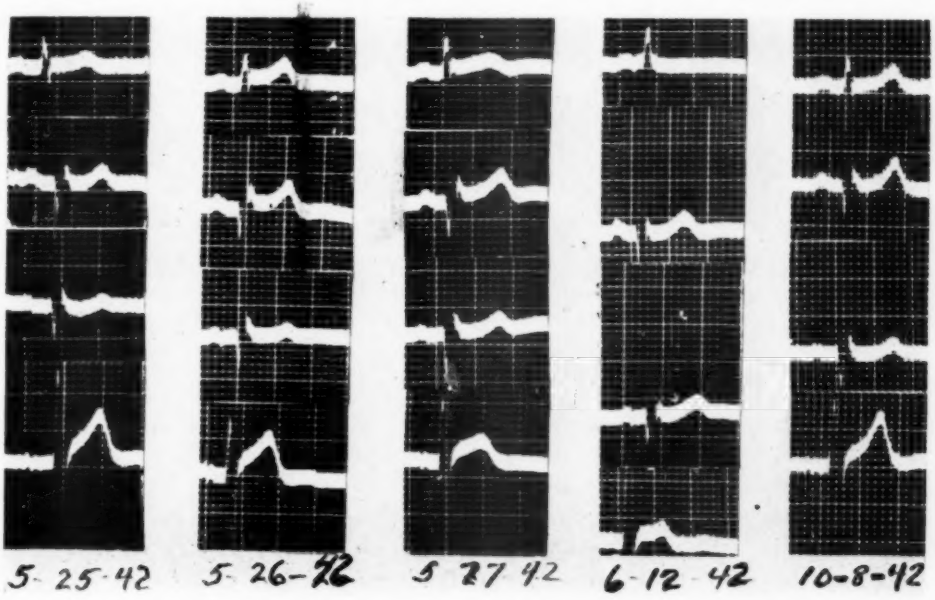

Fig. 2.—Case 3. On May 26 the S-T segments are elevated in Leads I, II, III, and CF_4. The T waves in Leads I and CF_4 are slightly inverted on May 27. Tracing is normal on October 8. Note that the Q waves in Leads II and III did not change throughout the series of tracings; these represent a normal variation for this individual.

same direction. Ordinarily, the QRS complexes are not affected, but in the presence of pericardial effusion, their amplitude may be lowered. Q waves do not occur as a result of pericarditis, in contrast to their presence in myocardial infarction. Q waves at times may be observed as a normal variation of an individual's tracing, but in these instances they do not change when serial tracings are taken. Auricular-ventricular conduction time remains normal, an important consideration in the differentiation from rheumatic fever.

The T waves may be abnormally tall and sharply pointed at onset, particularly in the precordial leads, but they soon become lower in amplitude and flattened. Usually after about a week they begin to invert and remain inverted from a few days to several months (Fig. 3). Inversion occurs in one or more leads;

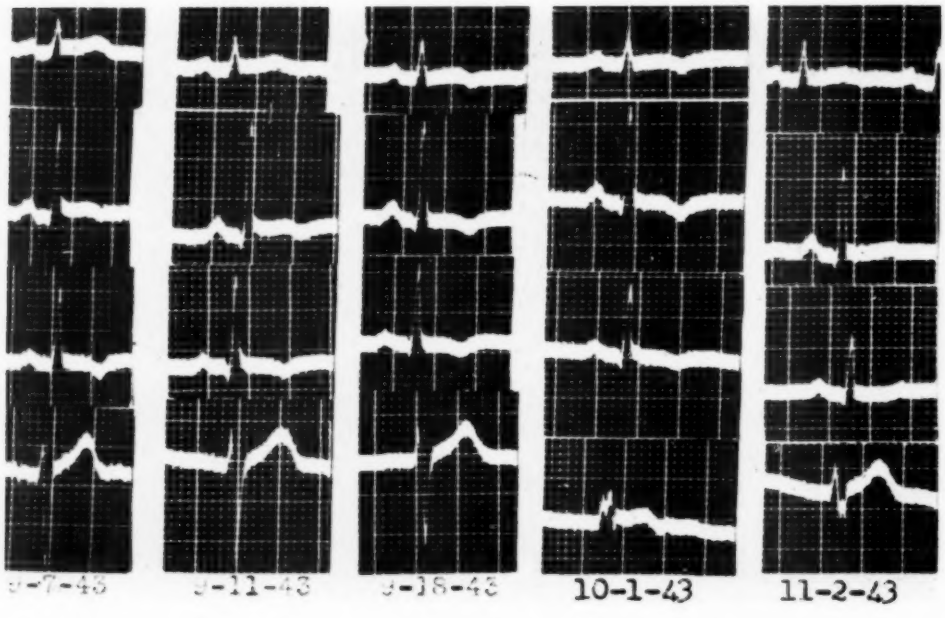

Fig. 3.—Case 6. The S-T segments are elevated in I, II, and III with inversion of T_2 and T_3 on September 7. On September 18 the T waves are inverted in I, II, and III. The precordial lead taken on October 1 was CF_2. This shows an M-shaped QRS and a QRS interval of 0.08 second. The single precordial lead of November 2 was apparently taken at the transitional zone. Tracing of November 2 shows residual flattening of the T waves in the standard leads.

at one time or another, the T waves may be inverted in all leads. Unless repeated tracings are taken, the stage of T-wave inversion may be missed. The changes in the T waves may fluctuate from day to day; one day the tracing may be abnormal, the next it may be normal, and on still another day, may again be abnormal. It has been suggested that this fluctuation is related to variations in the amount of edema or inflammation of the myocardium. This seems unlikely, and certainly the clinical manifestations do not parallel the electrocardiographic changes. It may be related to neurogenic influences.[2,8] The T-wave changes can be altered by the use of autonomic drugs, but the T waves do not completely

return to normal in individuals with vasomotor instability.[11] Generally, the electrocardiogram returns to normal after about four to eight weeks, leaving few or no residual changes.

CASE REPORTS

The following case reports are representative of the group.

CASE 2.—A 25-year-old soldier had been subject to repeated sore throat. He was hospitalized May 25, 1943, with acute tonsillitis and was returned to duty one week later. He continued to experience bouts of sore throat and on July 9 developed a feeling of indigestion and heaviness in the left upper abdomen with a sense of aching over the precordium. He felt as if belching would bring relief. The pain was aggravated by deep breathing and radiated to the left arm. There was some dyspnea. The temperature was 100.2° Fahrenheit. Nine days later there was a recurrence of sore throat with fever of 103° and recurrence of precordial pain. No friction rub was heard. The leucocyte count was 16,400. He was transferred to a general hospital with a diagnsois of anterior myocardial infarction. The initial tracing taken July 9, 1943, showed elevation of the S-T segments in Leads I, II, III, and CF_4 (Fig. 4). On July 10, 1943, there was late inversion of the T waves in Leads I, II, and CF_4. Two days later, on July 12, 1943, the tracing had returned to normal. A tracing on July 22, 1943, showed deep inversion of the T waves in Leads I, II, III, and CF_4. A tracing on Aug. 26, 1943, showed slight inversion of the T waves in Leads I and CF_4. The electrocardiogram was normal on Nov. 13, 1943. There were never any reciprocal changes, no Q waves, and no change in the auriculoventricular conduction time.

Comment.—The rapid fluctuation of the pattern is worthy of comment, particularly the return to normal two days after deep inversion of the T waves had been present. In our experience this is not uncommon in acute pericarditis. The patient developed a severe cardiac neurosis and he was subsequently discharged from the service.

CASE 4.—A 22-year-old soldier suddenly developed sore throat, generalized body aching, and fever on the day prior to his hospitalization. The following day he experienced a sudden severe, crushing substernal pain which radiated straight through to the back and seemed to limit his breathing. It was aggravated by deep inspiration and movements of the trunk. There was no history of antecedent rheumatic fever and no joint pains with the current illness.

At the time of admission to the hospital, his temperature was 103.4°F.; it subsequently became normal, except for a spike to 101° several days later. The heart, clinically, was normal. No pericardial friction rub was heard.

The leucocyte count was 12,400. The sedimentation rate was 30 mm. in one hour (Wintrobe). An electrocardiogram taken Feb. 5, 1943, showed elevation of the S-T segments in all leads (Fig. 5). The T waves were of increased amplitude, measuring 9.0 mm. in Lead II and 12 mm. in Lead CF_4; however, the tracing was overstandardized 2 millimeters. A tracing taken Feb. 6, 1943, revealed that the T waves were of lower amplitude and that the S-T segments were rectilinear in Leads I, II, and CF_4, being isoelectric in Lead III. On Feb. 24, 1943, the S-T segments had returned to the isoelectric level, and there was beginning inversion of the T waves in all leads, with slight lowering of the amplitude of the QRS complexes. A tracing on March 10, 1943, was entirely normal. The conduction time was never more than 0.20 second.

Comment.—Pericarditis in this instance was also related to an acute upper respiratory infection. The unusual feature of the case was the marked increase in amplitude of the T waves in all leads at the onset of the illness. In all other respects, the evolution of the electrocardiographic pattern conformed to the

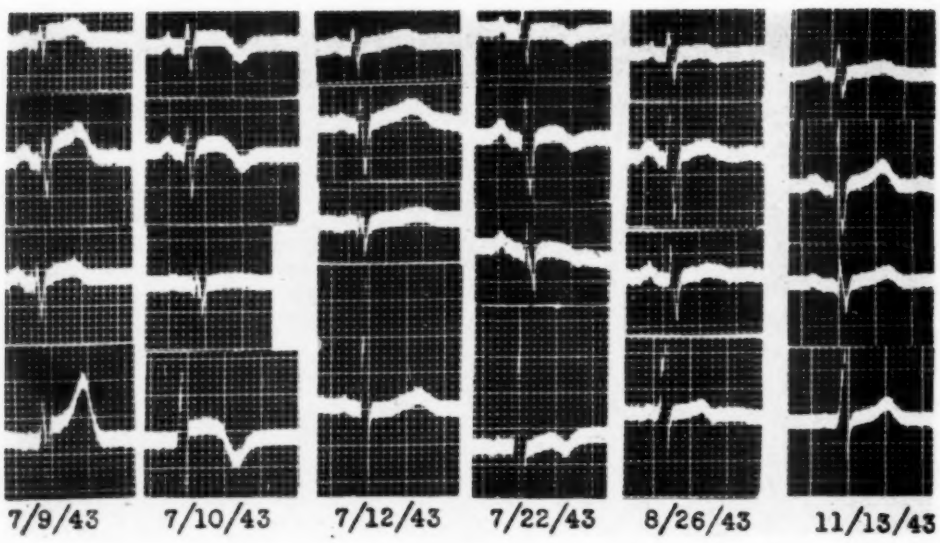

Fig. 4.—Case 2. The S-T segments are slightly elevated in all leads with beginning inversion of T_1 on July 9. A striking change has occurred on July 10 with deep inversion of T in I, II, and CF_4. Two days later the tracing has reverted to nearly normal. On July 22, the T waves are inverted in all leads, and on November 13, the tracing has returned to normal.

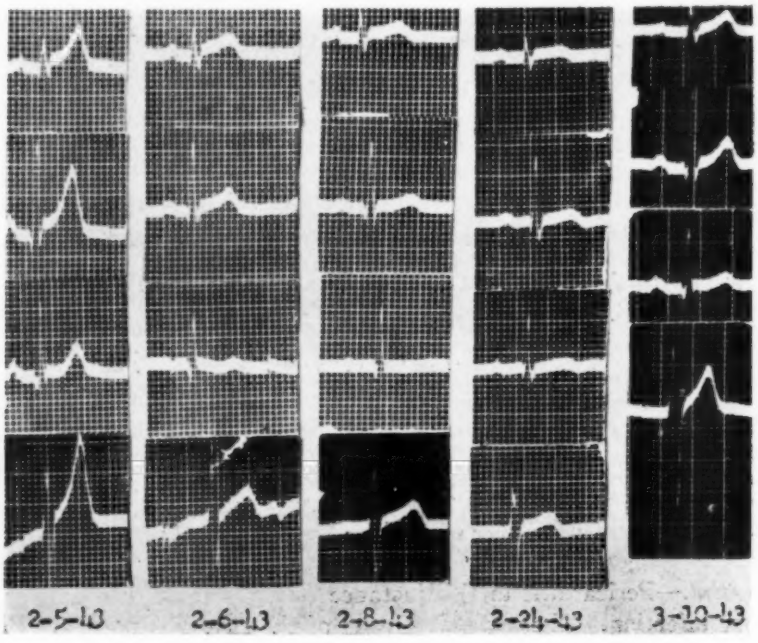

Fig. 5.—Case 4. The S-T segments are elevated in all leads on February 5. On February 24 the T waves are slightly inverted in all leads. The tracing of March 10 is normal.

criteria established for acute pericarditis. The S-T segments were elevated in all the leads in the initial record, and later the T waves showed beginning inversion in all leads. The tracing returned to normal in about one month.

CASE 5.—A 40-year-old soldier developed sudden severe precordial pain and syncope following an exhausting train trip. The pain was aggravated by deep inspiration and radiated to the left side of the neck. Turning in bed caused an increase in the discomfort. He was admitted to the hospital with a tentative diagnosis of coronary occlusion. There was a fever of 101°F. for two days, and a pericardial friction rub was heard during the second twenty-four hours. The leucocyte count was 10,000, and the sedimentation rate was 20 mm. in one hour (Wintrobe). One week later the sedimentation rate was normal. A tuberculin test using 0.01 mg. of purified protein derivative was negative. The pain subsided after twenty-four hours, and convalescence was uneventful.

An electrocardiogram made at the time of admission revealed an elevation of the S-T segments in all leads (Fig. 6). A tracing taken the next day showed progressive changes with some lowering of the amplitude of the T waves. A tracing taken April 2, 1944, showed beginning inversion of the T waves in Lead II with a horizontal S-T segment in Lead III. On April 6, 1944, the T waves were inverted in Leads I and IV and were flattened and slightly notched in Lead II. The S-T segments had become isoelectric in Leads I and III. On the following day, the T waves were inverted in Leads I and IV and were upright in Lead II, the S-T segments having returned almost to normal. An electrocardiogram taken May 3, 1944, was normal.

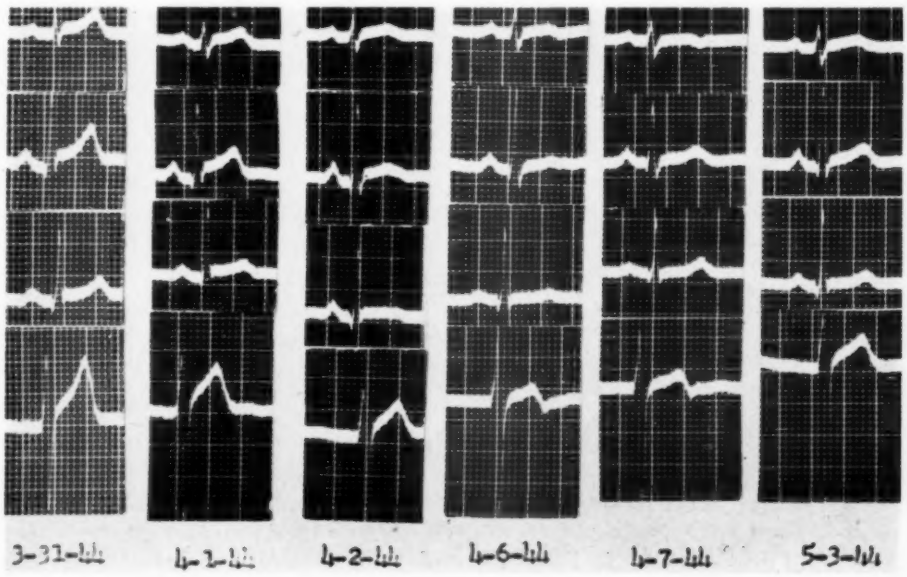

Fig. 6.—Case 5. The S-T segments are elevated in all leads on March 31. On April 6 the T waves are inverted in I and CF_4 with diphasic T_2, and the S-T segments have returned to the isoelectric line. Tracing of May 3 is normal.

Comment.—In this instance there was no history of associated respiratory infection. The associated syncope is an unusual manifestation of pericarditis. The admission diagnosis was coronary occlusion, but the evolution of the electrocardiographic pattern in serial records permitted the correct diagnosis of acute pericarditis to be made.

CASE 15.—A 46-year-old officer was admitted to the hospital March 1, 1945, complaining of pain in the left shoulder and a sense of pressure in the anterior chest which radiated to the neck. The patient had previously had an upper respiratory infection for about one month with an increase in severity of symptoms during the preceding week. Three days prior to admission he developed a nagging pain in the left shoulder, aggravated by deep breathing, change in position, coughing, and sneezing. On the next morning, there was a tightness across the front of the chest which extended into the neck. Subsequently, there was epigastric pressure which seemed to extend down from the chest. It was necessary for him to spend the night sitting up. He was feverish, had a "grippy feeling," and his teeth seemed to ache. There was no antecedent history of rheumatic fever. In 1943 he had had a similar episode of chest pain, following an upper respiratory infection, which had lasted two days. He had not been hospitalized at that time, and one electrocardiogram had been presumably normal.

The blood pressure was 110/60. The cardiac rhythm was regular, with a rate of 108 per minute. The patient appeared uncomfortable and protected the left shoulder from movement. The heart was of normal size and the sounds were of good quality. A faint, scratchy pericardial rub was heard at the third left intercostal space. There was slight tenderness over the left deltoid region. The leucocyte count was 10,450 with 71 per cent neutrophiles and 29 per cent lymphocytes. The urine was normal. The initial sedimentation rate was 1.2 mm. per minute by the Rourke-Ernstene method, gradually returning to normal during the next three weeks. A blood culture showed no growth. The Kahn test was negative. An x-ray film of the chest showed obliteration of the left costophrenic angle, with slight thickening of the pleura over apices of both lungs. An electrocardiogram taken March 1, 1945, three days after onset, revealed elevation of the S-T segments in Leads II, III, and CF_4 (Fig. 7). On March 3, 1945, the T waves had become

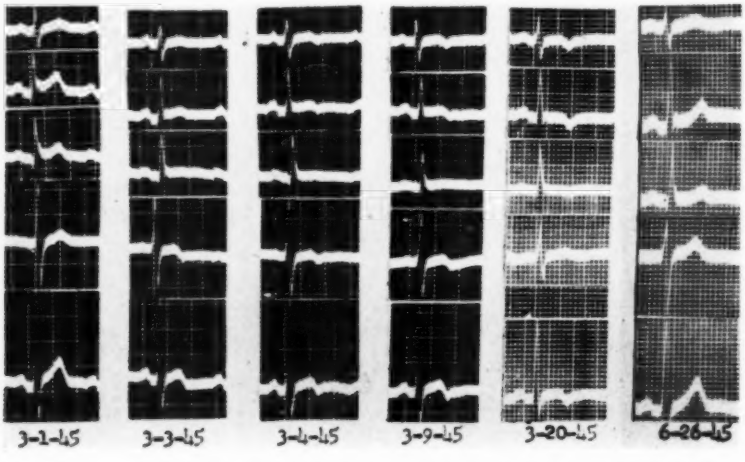

Fig. 7.—Case 15. On March 1, the S-T segments are elevated in II and III. On March 20, the T waves are inverted in Leads I, II, III, and CF_4 and are flattened in CF_2. The tracing of June 26 is normal, except for an unimportant degree of right axis deviation which is present throughout the series of tracings.

flattened in Leads I, II, and III and slightly inverted in Leads CF_4 and CR_4. The S-T segments were still elevated in Leads II and III, but were horizontal. On March 4, 1945, the T waves were inverted in Leads I, II, CF_4, and CR_4. On March 20, 1945, the T waves had become upright in CF_4. The tracing was within normal limits on June 26, 1945, except for a slight degree of right axis deviation which had been constant throughout the series of tracings. In September, 1945, the patient was readmitted to the hospital with another similar attack accompanied by transient elevation of the sedimentation rate and the serial electrocardiographic changes of acute pericarditis. He experienced one further episode in November, 1945, and was subsequently transferred to a general hospital for disposition.

DISCUSSION

During the same period in which these cases were observed, one of us (R. B. L.) observed a total of forty cases of pericarditis the etiology of which was as follows: "Non-specific," 15; rheumatic, 15; tuberculous, 4; neoplastic, 3; traumatic, 1; rheumatoid arthritis, 1; and acute disseminated lupus erythematosus, 1. There were, in addition, twenty-four cases of acute myocardial infarction in the age group from 20 to 40 years, and we were alert to the occurrence of this disease in young soldiers. The frequency of the "non-specific" type emphasizes its importance. It is probable that it is often overlooked in civilian life where the use of the electrocardiograph remains more limited.

The etiology of benign pericarditis is unknown. It is frequently, however, a sequel to upper respiratory infections.[17,18] This is probably the same type of pericarditis which has been reported as a complication of atypical pneumonia.[2,3,12,15] It may, perhaps, be the pericardial counterpart of the common variety of pleurisy associated with upper respiratory infections. Hargrove[16] reported a case of acute pericarditis due to *Streptococcus viridans*. Antistreptolysin titers were determined in two patients in the present series by Dr. Charles Rammelkamp.[20] These were normal, suggesting that hemolytic streptococcal infection and rheumatic fever were not responsible for the pericarditis. Dr. Rammelkamp studied two additional cases of acute "benign" pericarditis, and in each instance the antistreptolysin titers were normal. The possibility that this may represent an antigen-antibody reaction with sensitization of the pericardium and subsequent inflammatory reaction on exposure to bacterial antigen cannot be excluded. Three patients in this series gave a history of previous attacks, and one (Case 15) had a total of four attacks. This susceptibility to reinfection is similar to that seen in rheumatic fever.

That cases of acute pericarditis are still being confused with coronary disease is demonstrated by reports in the literature. Weinstein[13] reported ten cases of "atypical" coronary disease in young soldiers, and it seems probable that some of these were actually cases of pericarditis. Certainly Cases 2 and 5 of his series showed serial electrocardiographic changes of pericarditis. Case 2 was probably an instance of "benign" pericarditis, but Case 5 was probably one of rheumatic pericarditis. In the latter patient, there was an associated polyarthritis, and the antistreptolysin titer rose to 833 units. Clagett[14] reported a case of probable coronary disease with occlusion following fever therapy. A review of this case shows that the clinical and electrocardiographic findings were those of acute pericarditis, probably of the benign type. In discussing this patient he stated that the sudden change in the electrocardiogram during the second week of the illness, when the tracing returned toward normal and then on the next day suddenly reverted to an abnormal configuration, was more indicative of coronary thrombosis. In our experience, this is suggestive of pericarditis rather than myocardial infarction in which the changes remain relatively fixed once the pattern is established.

The importance of differentiation of pericarditis from myocardial infarction is obvious. The fact that a pericardial friction rub is not heard does not rule out the former; only eight of seventeen cases of pericarditis showed such a rub.

The frequency of the detection of a rub will depend upon how carefully and how frequently the patient is examined. The rub may be transient just as in myocardial infarction. Unless tracings are obtained early during the stage of S-T segment changes, it may be difficult to evaluate and differentiate the changes from those of a small myocardial infarct. The average age of patients with "benign" pericarditis is generally lower than that of patients with myocardial infarction. However, the increasing frequency with which myocardial infarction is recognized in young persons only serves to make the problem more difficult. Six of seventeen patients in the present series were considered as cases of probable coronary occlusion at the time of hospitalization, and the evolution of the electrocardiographic changes allowed the establishment of the proper diagnosis of pericarditis. Although none of the patients came to necropsy, the symptoms, course, and electrocardiographic changes gave strong evidence of pericarditis.

SUMMARY

1. Seventeen cases of acute pericarditis of benign type observed in the military service are reported.

2. Pain was the outstanding complaint, and in six instances a diagnosis of myocardial infarction had been made or had been entertained initially.

3. Serial antistreptolysin titers were determined on the serum of two patients and were found to be normal.

4. A tendency for recurrence of the disease was noted; three patients had more than one attack.

5. Rapid fluctuations of the changes in the electrocardiogram were at times noted.

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ACUTE MYOCARDIAL INFARCTION: DETAILED STUDY OF DICUMAROL THERAPY IN SEVENTY-FIVE CONSECUTIVE CASES

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THE addition of Dicumarol to the therapeutic armamentarium for the management of acute myocardial infarction increases the probability of significantly reducing the deaths and vascular complications accompanying the acute infarction. Although fatalities from acute myocardial infarction have been reduced through more rapid, accurate diagnosis and improved treatment, the mortality is still great enough to stimulate investigation of additional therapeutic agents. Dicumarol has been administered with excellent results as a prophylaxis for peripheral thromboembolic disease since 1942.[1] The most recent extension of the use of this anticoagulant has been in the management of acute myocardial infarction, a disease in which thromboembolic lesions are an important factor in the high mortality rate.

Prevalence of Thromboembolic Complications in Acute Myocardial Infarction.—There are numerous references in the medical literature which emphasize the importance of the tendency toward intravascular clotting as a complication after myocardial infarction. In a post-mortem study of 160 cases of acute coronary occlusion, Hellerstein and Martin[2] found that thromboembolic lesions were the chief cause of death in 15 per cent of the cases, and a contributory cause in an additional 12 per cent. Garvin[3] found mural thrombi present in the hearts of 67 per cent of patients dying of acute myocardial infarction. In reviewing the literature, Hellerstein and Martin[2] report that of 577 patients dying after an acute myocardial infarction, 10 per cent died of pulmonary embolism. Clinical evidence of thromboembolic disease accompanying the occlusive coronary episode has been reported by numerous investigators. Master and associates[4] observed 500 patients with acute myocardial infarction. They reported a 6 per cent mortality due to clinical embolism. Woods and Barnes[5] found massive pulmonary embolism to be the cause of death in six of their sixty patients with acute coronary occlusion. Nay and Barnes[6] observed thirty-seven instances of thromboembolic lesions occurring in 100 patients with acute coronary thrombosis. Hellerstein and Martin,[2] in the most recent review of this subject, report 185 instances

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(12 per cent) of clinical embolism in 1,605 cases of myocardial infarction. Thus, there is ample evidence of the role of intravascular clot formation complicating the occlusive episode and thereby increasing the mortality rate.

Use of Anticoagulants in Acute Myocardial Infarction.—In 1939 Solandt and associates[7] reported that heparin prevented the occurrence of mural thrombi in dogs whose coronary arteries were occluded experimentally. It was not until 1946 that the first of four papers[8-11] was published in which Dicumarol was used in the management of acute myocardial infarction in series of significant numbers. The authors of these papers reported a reduction in the mortality rate and in the number of thromboembolic episodes when Dicumarol was added to the conventional methods of treatment. Nichol and Page, Jr.,[8] used Dicumarol in fifty instances of acute myocardial infarction. There was one case of clinical embolism. No fatalities occurred in the twenty-six patients suffering their first attack. Among the other patients there were eight deaths. Post-mortem examination of six of these cases failed to reveal any mural thrombi, peripheral embolism, or pulmonary embolism. Peters and co-workers[9] reported two deaths in fifty cases of acute coronary thrombosis treated with Dicumarol as compared with a control series of sixty patients treated without Dicumarol in which thirteen deaths occurred. Of the thirteen fatalities, six were due to embolism. Wright[10] used Dicumarol in the management of seventy-six patients with acute myocardial infarction. He found that the mortality was reduced to one-third of that anticipated with conventional therapy. Fifty patients with acute myocardial infarction treated with Dicumarol were compared by Parker and Barker[11] with 100 similar patients not given Dicumarol. They found that the incidence of vascular complications was 4 per cent following Dicumarol therapy and 37 per cent in the control group. The mortality rate was reduced from 13 per cent in the control series to 10 per cent in their series given Dicumarol.

In summary, the number of patients treated with Dicumarol totaled two hundred twenty. There were thirty deaths, or a mortality rate of 14 per cent. This is an excellent result, especially when one takes into account the fact that forty-three of Wright's patients had repeated attacks of coronary occlusion, embolic phenomena, or both (Table I).

TABLE I. RESULTS OF TREATMENT WITH DICUMAROL IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

SOURCES	NO. OF PATIENTS	DEATHS	PER CENT DEATHS
Nichol and Page[8]	44	8	18
Peters, Guyther, and Brambel[9]	50	2	8
Wright*[10]	76	15	20
Parker and Barker[11]	50	5	10
Our series	75	7	9
Total	295	37	12.5

*Forty-six of the cases of Wright's series were deliberately selected because they had complications known to be associated with a high mortality rate. This fact may very well account for the higher mortality rate in his series.

The experience which has been cited constitutes a rational basis for the use of Dicumarol in the management of acute myocardial infarction in an attempt to: (1) prevent further thrombosis in the coronary arteries and to inhibit further extention of the existing thrombus; (2) avert phlebothrombosis, thrombophlebitis, and pulmonary embolism; (3) prevent the formation of a mural thrombus or the extension of already formed thrombi; and (4) prevent peripheral arterial thrombosis.

PURPOSE OF STUDY

In this report we wish to present the results with Dicumarol therapy in relation to the incidence of vascular complications in acute coronary thrombosis and the overall mortality rate in seventy-five consecutive patients. These results are compared with those of a control series consisting of the last 100 patients with acute myocardial infarction managed conventionally on the same service at Lincoln Hospital before the advent of Dicumarol therapy.

ANALYSIS OF PATIENTS

The patients in both the control series and in the series treated with Dicumarol were ward patients at Lincoln Hospital, one of the municipal hospitals of New York City. The subjects were white, Negro, and Puerto Rican patients of the lowest income group, and were admitted to the hospital within the last two and one-half years. All the patients in both series had well-defined clinical, electrocardiographic, and other laboratory evidence of acute myocardial infarction. The management of both series of patients was the same except for the use of Dicumarol in one group. In the series of patients given Dicumarol, the youngest patient was 38 years of age and the oldest, 80 years. The average age was 60 years in the series given Dicumarol as compared with an average age of 58 years in the control series. Table II indicates the distribution as to age, sex, mortality, and thromboembolic complications of the patients in both the control series and the series receiving Dicumarol.

TABLE II. DISTRIBUTION OF SERIES GIVEN DICUMAROL AND CONTROL SERIES ACCORDING TO AGE, SEX, MORTALITY, AND THROMBOEMBOLIC LESIONS

AGE (YEARS)	SEX				MORTALITY				THROMBOEMBOLISM			
	DICUMAROL		CONTROL		DICUMAROL		CONTROL		DICUMAROL		CONTROL	
	M	F	M	F	M	F	M	F	M	F	M	F
30-39	1	0	2	0	0	0	0	0	0	0	0	0
40-49	10	3	16	6	0	1	3	1	0	1	4	1
50-59	18	5	22	10	0	1	5	4	0	1	6	3
60-69	18	8	22	7	0	2	11	5	0	0	4	1
70-79	7	4	8	4	2	1	4	2	0	1	1	1
80-89	1	0	2	0	0	0	0	0	0	0	0	0
90-99	0	0	1	0	0	0	0	0	0	0	0	0
Total Per Cent	55	20	73	27	2	5	23	12	0	3	15	6

In the Dicumarol series, thirty-six patients had had a previous hypertension, twenty-one had had one previous episode of acute myocardial infarction, one had had two previous episodes, and another had had three previous episodes of myocardial infarction. A previous history of angina pectoris was obtained in twenty-five patients. Congestive failure was present in nine cases. Two patients had had previous episodes of cerebrovascular occlusion. There were forty-two instances of anterior myocardial infarction, and thirty-two of posterior myocardial infarction. Nonvascular complications in these patients were: diabetes mellitus in eleven, rheumatic heart disease in two, chronic cholecystitis in two, latent syphilis in two, syphilitic aortitis and syphilitic aneurysm in one, and renal insufficiency, diabetic ketosis, carcinoma of the breast, mixed tumor of the parotid gland, carcinoma of the prostate, and bronchiectasis, each present in one patient.

Contraindications to Dicumarol Therapy.—In the series of patients given Dicumarol no attempt was made to select certain patients because of the mildness or severity of their reaction to the acute myocardial infarction. The contraindications to Dicumarol in the management of acute myocardial infarction were as follows: (1) hypoprothrombinemia due to severe hepatic insufficiency; (2) blood dyscrasias with bleeding tendencies; and (3) ulcerative lesions of the gastrointestinal tract.

It should be remembered that patients receiving quinine[12] or salicylates[13] may have elevated prothrombin times, and that they may show a marked response to the usual dose of Dicumarol. One patient with severe renal insufficiency was treated with Dicumarol in reduced dosage. The only patients with acute myocardial infarction who were not included in either the control series or in the series given Dicumarol were those moribund patients who died within forty-eight hours after admission to the hospital. The reason for their exclusion from either series was the known fact that Dicumarol does not usually cause an effective hypoprothrombinemia before forty-eight hours. The inclusion of such patients in the series studied would not give additional information as to the effectiveness of anticoagulant therapy in acute myocardial insufficiency. There were three such moribund patients who were given one to two doses of Dicumarol and who died within forty-eight hours after admission. These deaths occurred before the prothrombin concentration could be reduced to an effective anticoagulant level. A study of such a series is in progress.

METHOD

Quick's method[14] of prothrombin determination of undiluted plasma was used. Vacuum desiccated rabbit lung served as the thromboplastic agent and was highly satisfactory. The normal prothrombin time was 14 to 16 seconds. Dicumarol was given in order to reduce the prothrombin concentration to between 10 and 30 per cent of normal. The prothrombin was maintained at this reduced concentration throughout the period of complete bed rest. In this method, using rabbit lung as the source of thromboplastin, a prothrombin time of 28 seconds represents a 30 per cent concentration of prothrombin; 35 seconds represents 20 per cent concentration; and 48 seconds represents 10 per cent prothrombin concentration.

In administering Dicumarol every effort was made to obtain an anticoagulant effect in the blood as soon as possible after acute myocardial infarction was diagnosed. Dicumarol was given to the patient according to the following schedule: (1) When the initial prothrombin time was normal, 300 mg. Dicumarol was given to the patient. (2) On the following day, if the prothrombin time was lower than 28 seconds, 200 mg. of Dicumarol was administered; if the prothrombin time was between 28 and 35 seconds, the patient received 100 mg. of Dicumarol; if the prothrombin time was above 35 seconds, Dicumarol was not given. (3) Following the second prothrombin determination, the prothrombin time was taken every forty-eight hours. Dicumarol was given in 50 to 100 mg. doses when the prothrombin time was between 35 and 48 seconds, according to the individual patient's sensitivity to the drug. If the prothrombin time rose above 48 seconds, Dicumarol was not administered. If the prothrombin time went below 28 seconds, larger doses than the maintenance doses of 50 to 100 mg. were given. On the alternate days, when prothrombin determinations were not performed, Dicumarol was given in doses of 50 milligrams. This helped to maintain the prothrombin at an effective anticoagulant concentration without marked alterations in prothrombin concentration from day to day.

If there was any evidence of bleeding, such as microscopic hematuria, purpuric spots in the skin, rectal bleeding, and so forth, Dicumarol was discontinued and 50 mg. synthetic vitamin K (menadione bisulfite) was given intravenously.[15] When the prothrombin time rose above 48 seconds (below 10 per cent prothrombin concentration), Dicumarol was discontinued until the prothrombin concentration returned to an effective anticoagulant level. When bleeding occurred in patients whose prothrombin concentration was below 10 per cent, intravenous synthetic vitamin K controlled the bleeding and increased the prothrombin concentration to above 10 per cent of normal within twenty-four hours. Dicumarol therapy was then resumed.

We have found that patients differ from one another in their response to Dicumarol. The same patient may show variations in sensitivity to the drug at different times. The Dicumarol schedule had to be varied in a number of instances in order to obtain and maintain an effective anticoagulant level. The best example of this is described in the following case report.

CASE 40.—M. E., a 69-year-old white woman, was known to have had diabetes for ten years and hypertensive heart disease for one year. Her diabetes was controlled by diet and protamine zinc insulin. Two weeks before admission the patient had a nasopharyngitis which continued up to the time of admission. One week before admission she became drowsy and the drowsiness increased during the ensuing week. In the last week before admission she developed generalized pruritus and vomited several times daily. On admission her temperature was 100.4° F.; pulse, 110; respirations, 24; and blood pressure was 135/75. Urinalysis and determination of blood carbon dioxide combining power substantiated the diagnosis of diabetes mellitus with ketosis. On admission physical examination revealed the patient's heart to be enlarged. The point of maximum intensity was 2.0 cm. to left of the mid-clavicular line in the fifth intercostal space. The heart sounds were distant and of poor quality. An electrocardiogram revealed an acute anterior infarction. Two hundred milligrams of Dicumarol were given instead of the usual 300 mg. because the initial prothrombin concentration was 40 per cent of normal. With this single dose of Dicumarol the patient's prothrombin concentration reached an effective anticoagulant level in twenty-four hours and remained there for nine days without additional Dicumarol. On the tenth

day the prothrombin concentration rose above the effective anticoagulant level. A second dose of Dicumarol, this time 100 mg., was given. In twenty-four hours the prothrombin concentration was again reduced to an effective anticoagulant level, which was maintained for seven days. At this time, the patient's diabetes was well under control. For the remaining fifteen days that she received Dicumarol, the patient required 50 to 100 mg. every other day in order to maintain an effective prothrombin concentration. Liver function tests were normal. The patient recovered and left the hospital after six weeks with mild angina pectoris on effort.

Complications Arising From Dicumarol Therapy.—The only complication that may occur from the use of Dicumarol is hemorrhage. In our series of seventy-five patients given Dicumarol there were no major hemorrhagic episodes. None of the patients required blood transfusions. Two patients had minor rectal bleeding episodes from internal hemorrhoids when their plasma prothrombin levels dropped below 10 per cent. One patient had a macroscopic hematuria for twenty-four hours. These patients received 50 mg. of synthetic vitamin K (menadione bisulfite) intravenously, and within twenty-four hours the bleeding had ceased. The patients were then continued on Dicumarol therapy, thereafter being maintained closer to a prothrombin concentration of 30 per cent than to 10 per cent. They had no other bleeding episodes, made uneventful recoveries; and were discharged from the hospital. When Dicumarol therapy is guided by prothrombin determinations performed every twenty-four to forty-eight hours, it is our opinion that there is little danger of major hemorrhagic episodes occurring in patients with acute myocardial infarction. We have seen no untoward effects in our series of seventy-five cases, due, as we insist, to careful laboratory control.

RESULTS

In the control series there were twenty-one instances of thromboembolic lesions occurring in the patients with acute myocardial infarction. There were ten instances of pulmonary embolism, four of thrombophlebitis, four of cerebral thromboembolic disease, and three instances of arterial embolism to the leg. The series of patients given Dicumarol included only three instances of thromboembolic disease complicating the acute myocardial infarction after the administration of Dicumarol. There were thirty-five deaths in the control series and seven deaths in the series given Dicumarol. Thus, there was a mortality rate of 9 per cent in the series given Dicumarol as compared with a mortality rate of 35 per cent in the control series. The incidence of thromboembolic lesions was 4 per cent in the series given Dicumarol and 21 per cent in the control series. This is an impressive and significant reduction in the incidence of intravascular thrombosis and in the per cent of fatalities. Three patients in the series given Dicumarol had signs and symptoms of thrombophlebitis before Dicumarol was administered. However, they showed no extension of intravascular clotting after Dicumarol was administered and recovered uneventfully. One patient had a pulmonary embolism following the acute myocardial infarction. He was then placed on Dicumarol. No further episodes of embolism occurred, and he recovered uneventfully. One patient suffered a cerebral embolism with hemiplegia as a complication of an acute coronary occlusion. He was then placed on

Dicumarol and there were no recurrences of thromboembolic episodes. He left the hospital with moderate paresis of the right arm and right leg.

Analysis of the Mortality Group.—In the clinical analysis of the seven deaths that occurred in this series of seventy-five cases given Dicumarol, it was found that three patients died of marked congestive heart failure, two in the convalescent period, within a month, and one at the end of seventh week; two patients died of cerebral thrombosis; one patient died of uremia; and one patient died suddenly twenty-seven days after the acute myocardial infarction. The latter episode was probably due to ventricular rupture with acute pericardial tamponade. The patient was a 70-year-old man who had a two-year history of hypertension. His course in the hospital was uneventful until the twenty-seventh day following the acute coronary occlusion. While eating his evening meal, he suddenly became comatose. He could not be aroused. His heart sounds were very rapid and distant and ceased one minute after he lost consciousness. The two patients who died of cerebral thrombosis were women. Both were diabetic patients of long standing, which was rather significant in the evaluation of the intercurrent lesion. Their case reports follow.

CASE 27.—M. E., a 48-year-old Negro woman, had had hypertensive heart disease for nine years and diabetes mellitus for five years. She had had three previous episodes of acute myocardial infarction. Five hours before admission the patient had a crushing substernal pain which radiated into the right shoulder and right arm and was not relieved by nitroglycerin. On admission her temperature was 99.5° F.; pulse, 100; respirations, 24 per minute; and blood pressure was 170/110. The heart sounds were distant and the heart was enlarged to the left. The point of maximum intensity was on the anterior axillary line in the sixth intercostal space. A diagnosis of acute myocardial infarction was made. An electrocardiogram revealed an acute posterior infarction. She was started on 300 mg. of Dicumarol and ninety-six hours later her prothrombin concentration was at an effective anticoagulant level of 30 per cent. This was seven days after the occlusion. On her eighth hospital day she became irrational, disoriented, and submaniacal. On the twelfth day a mild right facial weakness was first noticed. This gradually increased in severity. Three days later a concomitant left hemiplegia developed. Her field of consciousness slowly narrowed; disorientation increased; she became semicomatose and expired seven days later. The administration of Dicumarol, therefore, could not be continued regularly or effectively.

CASE 32.—R. E., a 72-year-old white woman, had had mild diabetes mellitus for thirty years. There was no history of hypertension. Her diabetes was controlled on diet alone. Four years before the present admission, she had been hospitalized for an acute myocardial infarction. Two years before admission she developed a cerebral thrombosis and was hospitalized for ten weeks. She still had right facial weakness and paresis of the left hand at the time of this admission. For the previous nine months she had been taking daily rations of digitalis for her failing heart. The patient was admitted to the hospital because of a three-day history of severe pressing substernal pain, radiating to the left shoulder and left arm. On admission her temperature was 102° F.; pulse rate, 102; and ventricular rate, 120 per minute; respirations, 28 per minute; and blood pressure, 110/60. Examination of the heart revealed it to be normal in size. The sounds were distant and poor in quality, and auricular fibrillation was present. The electrocardiogram revealed a recent posterior myocardial infarction. She was started on 300 mg. of Dicumarol on the second hospital day. On the fifth hospital day when the prothrombin concentration had reached an effective anticoagulant level of 30 per cent for the first time, the patient developed paresis of the left arm. She did not complain of headache nor was there evidence of nuchal rigidity. The mild disorientation which was present prior to this episode increased rapidly, so that Dicumarol could not be administered effectively. Her chest film revealed a heart of normal size. Her blood pressure at this stage was 150/80. She died on the twelfth hospital day.

Comment: Both cases (M. E. and R. E.) had previous acute coronary occlusions in addition to long-standing diabetes mellitus. In Case 32, R. E., the prothrombin concentration reached 30 per cent the same day on which the cerebral lesion developed. If the cerebral thrombosis had not occurred at the time it did, it is possible that it might have been prevented once the effective prothrombin level had been established. However, it probably would have then occurred soon after the prothrombin concentration was allowed to return to normal. In Case 27, M. E., the prothrombin was not at an effective anticoagulant level until the seventh day following the acute coronary occlusion. It is very likely that in this case, also, the cerebral lesion developed on the same basis. The effective prothrombin level had hardly been established in either case when these lesions developed. The similarity in the course of both these diabetic patients is worthy of note.

Permission for autopsy was not obtained in the seven patients in the Dicumarol series who died. A post-mortem examination was performed, however, on Case 22, F. L., a 55-year-old white man who had an acute anterior myocardial infarction, syphilitic aortitis, and a syphilitic aneurysm of the ascending aorta. He recovered from his acute occlusive episode and was discharged from the hospital after six weeks, only to be readmitted one month later in marked congestive heart failure. He died after forty-eight hours, despite therapy. Post-mortem examination revealed an enlarged heart weighing 500 grams. There was hypertrophy and dilatation of the left ventricle, with marked atherosclerosis and narrowing of the left anterior descending coronary artery. There was an almost completely healed myocardial infarct in the anterior wall of the left ventricle. There was no evidence of mural thrombi, ventricular aneurysm, pulmonary embolism, or any systemic thromboembolic lesions.

In the control series post-mortem examinations were performed on nine patients. In examination of these nine patients, five instances of pulmonary embolism, five instances of peripheral thromboembolic lesions, and four mural thrombi were found.

DISCUSSION

Askey and Neurath[16] reported that digitalis was contraindicated in acute myocardial infarction. They found that though the danger of sudden death from myocardial rupture or from ventricular fibrillation was not significantly increased when digitalis was used, there was a marked rise in the incidence of clinical embolism. They reported thirty-one deaths in thirty-two patients with acute myocardial infarction complicated by congestive heart failure with auricular fibrillation and treated with digitalis. In thirteen of these thirty-one patients, death was due to arterial embolism. Peters and associates[9] reported nine deaths, most of them due to embolism, in seventeen patients with acute myocardial infarction complicated by congestive heart failure and treated with digitalis. In their series of fifty patients with acute myocardial infarction treated with Dicumarol, there were eight patients with congestive heart failure who required digitalis therapy. Only one of these eight patients died. Thromboembolic lesions did not occur in any of these patients.

The findings in our study conform with those of Peters and co-workers.[9] In our control group of 100 patients with acute myocardial infarction, seventeen required digitalis for congestive failure. Nine (53 per cent) of these seventeen patients died. Of these nine patients, five had signs of embolism. In the series treated with Dicumarol there were fifteen patients with congestive heart failure severe enough to require digitalis. Three of these (20 per cent) died in marked congestive failure with no signs of thromboembolic complications.

If digitalis increases the coagulability of the blood, as stated by De Takats and associates,[17] Massie and co-workers,[18] and Peters and associates,[9] then the results obtained by us and by others[9] in small groups of patients with acute myocardial infarction complicated by congestive heart failure and treated with digitalis without the occurrence of thromboembolic lesions suggest that Dicumarol can oppose effectively the thrombogenic property of digitalis which increases the tendency for embolism. We feel Dicumarol should be administered to patients with acute myocardial infarction who are in congestive failure and are receiving digitalis.

SUMMARY

Dicumarol was used in the management of seventy-five consecutive ward patients with acute myocardial infarction. The mortality rate was 9 per cent and the incidence of thromboembolic lesions was 4 per cent. These results reveal a decided improvement over the results obtained in a control series of 100 patients with acute myocardial infarction treated with conventional therapy. In the latter series there was a mortality rate of 35 per cent and an incidence of thromboembolic lesions of 21 per cent. There were no serious complications attributable to the use of Dicumarol.

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Clinical Reports

NEOPLASTIC METASTASIS TO THE HEART*

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METASTATIC involvement of the heart by tumor growth is not too infrequent. Statistical studies of large series of autopsies by several authors indicate an incidence varying from 0.24 to 1.06 per cent.[1-5] The largest series of cases reported in the literature is that of Scott and Garvin[2] who found 118 instances of metastatic involvement of the heart in 1,082 cases of malignant disease in a series of 11,000 autopsies at Cleveland City Hospital during a period of twenty years. They stated that "metastasis to the heart occurred from neoplasms involving practically every organ of the body."

Comprehensive reviews of the reported cases in the literature were made by Yater[6] in 1931 and by Lisa and his associates[7] in 1941 and will not be repeated here. The purpose of the present paper is to record an instance of an unusually extensive involvement of the heart by metastatic tumor in a case of malignant melanoma; in addition, five other cases of invasion of the heart by secondary metastases are briefly described.

CASE REPORTS

CASE 1.—A 48-year-old white man was admitted to the hospital on Dec. 13, 1946, complaining of daily chills, fever, and sweating accompanied by soreness and aching pains in the muscles, joints, and bones for the past six weeks; the bones felt as if they were "bursting." Two years prior to admission a black mole on the left wall of the chest was removed with an "acid solution." The wound healed and there was no apparent local recurrence. He was well until six weeks before admission when he was taken ill with a sudden chill followed by fever and sweating, and accompanied by aching pains in the muscles, joints, and bones. He had marked anorexia but no nausea or vomiting. These symptoms had recurred almost daily, and increased gradually in severity; at times he was delirious. Three weeks before admission a tender "spot" developed in the right upper quadrant of the abdomen; two weeks before admission he noticed tarry stools, and one week before admission he developed a cough productive of blood streaked sputum.

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The patient was poorly nourished and appeared to be acutely and chronically ill. Numerous small, hard nodules were palpable in the subcutaneous tissues over the entire body surface; many of these nodules appeared bluish in color. The supraclavicular nodes were moderately enlarged and tender. There was generalized muscle tenderness. The heart was not considered to be enlarged, the rhythm was regular, rate 116 per minute, and the sounds were of good quality; a faint systolic murmur was heard over the base; the blood pressure was 108/64. The liver was palpated 6.0 cm. below the costal margin and was very tender; there was generalized tenderness of the entire abdomen but no other organs or masses were noted. Roentgen examination of the chest revealed slight enlargement of the cardiac shadow. Complete blood count revealed 3,740,000 red blood cells, 16,250 white blood cells, 13.6 grams of hemoglobin, 85 per cent polymorphonuclear leucocytes, 10 per cent lymphocytes, 4 per cent monocytes, and 1 per cent basophiles. Urinalysis showed 0 to 2 white blood cells, 1 to 3 red blood cells per high-power field, and a few waxy, hyaline, and granular casts. The blood Kahn reaction was negative. The diagnosis of malignant melanoma with generalized metastases was made. Biopsy of one of the subcutaneous nodules confirmed this diagnosis.

The patient's temperature fluctuated between 98 and 101°F., and at times reached 104 °Fahrenheit. The blood culture was negative; a blood smear did not show malarial parasites. No acid-fast bacilli were found in the sputum. Agglutination tests for typhoid, paratyphoid, brucellosis, and tularemia were negative.

The patient's heart rate was rapid and fluctuated between 98 and 134 per minute, the higher rates occurring coincidentally with the rises in temperature. The anemia and weakness gradually increased in severity and the patient died on Dec. 26, 1946, thirteen days after admission to the hospital.

Necropsy.—Widespread nodular metastases were found in the lungs, pleura, heart, liver, gall bladder, spleen, pancreas, adrenals, kidneys, ureters, urinary bladder, prostate, testes, thyroid, brain, bones, lymph nodes, peritoneum, mesentery, serosa of the gastrointestinal tract, and diaphragm.

The pericardial cavity contained approximately 200 c.c. of clear straw-colored fluid. The pericardium itself presented no abnormalities. The heart weighed 550 grams. The surfaces of the heart were studded with conglomerated nodular infiltrations which varied from pinkish-white to grayish-white in color. The endocardial surfaces of the auricles and ventricles were extensively infiltrated with conglomerate masses of variously sized nodules involving all of the musculi pectinati, trabeculae carneae, and papillary muscles. These infiltrations were more marked in the right chambers (Fig. 1). A few nodules were seen scattered over some of the chordae tendineae and the leaflets of the mitral and tricuspid valves. The cusps of the pulmonic and aortic valves appeared normal. The foramen ovale was closed. On section, the wall of the left ventricle measured 2.8 cm. and that of the right ventricle, 1.0 cm. in thickness; the cut surfaces were pinkish-brown in color, friable, and extensively infiltrated by variously sized tumor nodules which appeared grayish in color. The ostium of the right coronary artery presented sclerotic plaques; the coronary vessels were patent throughout their entire course. The aorta presented numerous sclerotic plaques, but its elasticity was fairly well preserved.

Microscopic examination of several sections taken from the interventricular septum, left and right ventricles, and auricles showed diffuse and extensive involvement of the epicardium, myocardium, and endocardium by tumor growth. The tumor cells were arranged in solid nodular masses and columns more or less completely replacing the cardiac muscle in many areas. In the relatively uninvolved zones the cardiac muscle bundles showed fragmentation, indistinct striations, replacement fibrosis, and a moderate degree of congestion and edema. Many venous and lymph vessels were seen to contain tumor cells. The tumor cells were fairly uniform in appearance; they presented large vesicular nuclei surrounded by a varying amount of faintly staining eosinophilic cytoplasm; many mitotic figures were noted. No melanin pigment was seen in these cells (Figs. 2 and 3).

CASE 2.—A 39-year-old white man in 1940 noted a small, dark "birthmark" just below the left axilla; this grew in size slowly so that his clothes irritated it causing it to bleed. The growth

was fulgurized by his physician in 1942. In October, 1945, he noted a small swelling in the left axilla. In July, 1946, small nodules appeared over the entire body; the patient began to lose weight, became weak, and noted shortness of breath. He applied for admission to the hospital on Oct. 26, 1946, because two days previously his right arm and right leg had become weak and lifeless.

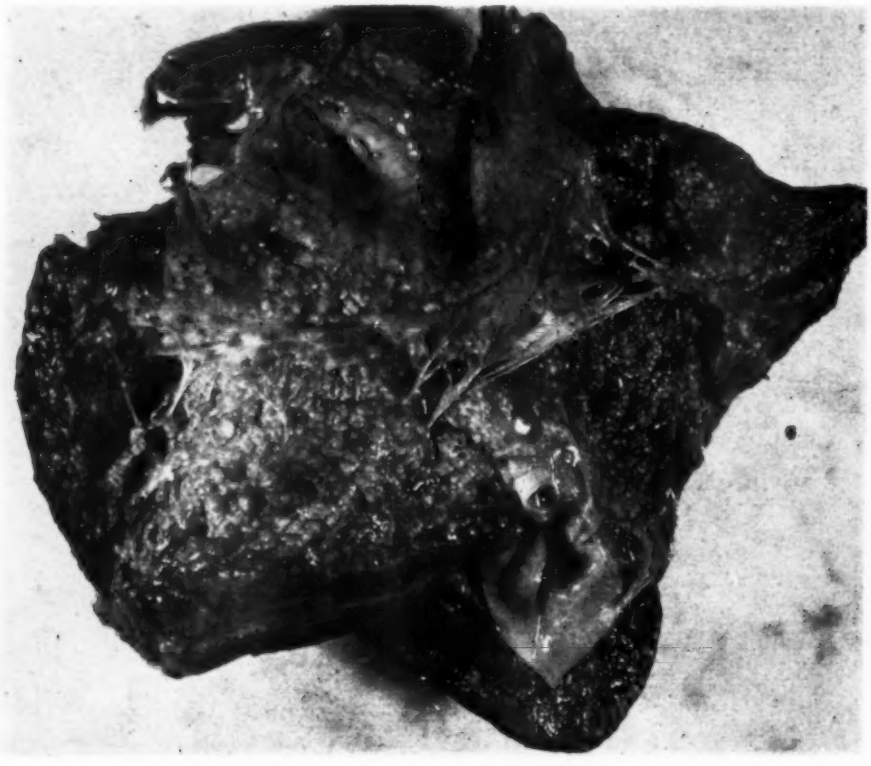
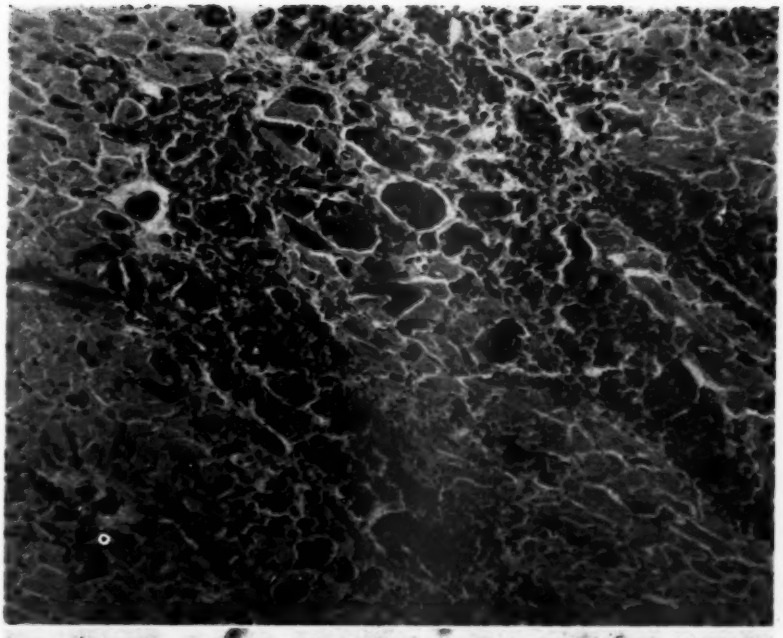


Fig. 1.—Case 1. Open right ventricle. Note the diffuse nodular involvement of all parts of the heart.

Numerous subcutaneous nontender nodules were found distributed over the entire body surface; the skin over some of these nodules appeared purplish in color. The heart was not enlarged; the rhythm was regular, the rate 72 per minute, and no murmurs were audible. The blood pressure was 120/76. The liver was nodular, slightly tender, and was felt three fingerbreadths below the costal margin. There was spastic paralysis of the right upper and lower extremities with hyperactive reflexes and positive plantar reflex. Roentgen examination of the chest showed multiple nodular infiltrations throughout both lung fields; the heart was not enlarged.

On the evening of October 29 the patient had a sudden clonic seizure involving the right upper and lower extremities followed by loss of consciousness and stertorous breathing. The entire episode lasted approximately two hours. On the following morning the patient was conscious and alert, but a slight hesitancy in his speech was observed and he had difficulty in choosing the proper words. His condition gradually deteriorated and he died on Dec. 4, 1946. During the period of hospitalization the temperature remained between 98 and 99°F. with occasional rises to 101°F. in the evening. The heart rate varied between 80 and 100 per minute with occasional rises up to 110 and 116. At no time was any definite evidence of cardiac failure noted.

Fig. 2.



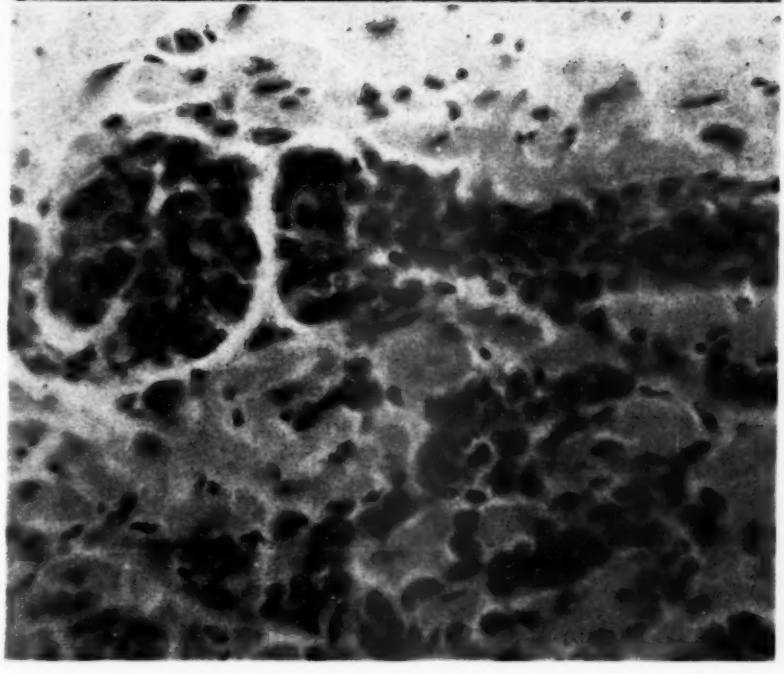


Fig. 3.

Fig. 2.—Case 1. Microscopic section of wall of the left ventricle (medium power). Note the nodular and columnar arrangement of the invading tumor cells.

Fig. 3.—Case 1. High-power view of section from the interventricular septum. Note the uniform appearance of the tumor cells.

Necropsy.—Numerous subcutaneous nodules, varying in size from match-head to 3.0 cm. in diameter, were distributed throughout the entire body surface. The skin over most of these nodules appeared brownish-blue. Nodular metastases were found in the lungs, pleura, heart, liver, pancreas, adrenals, kidneys, brain, peritoneum, mesentery, and lymph nodes. The heart weighed 260 grams; several tumor nodules of varying size were found in the walls of both auricles and the left ventricle. Histologic examination showed malignant melanoma.

CASE 3.—A 52-year-old white man was well until March, 1946, when he developed "pneumonia." Bronchoscopic examination revealed inoperable cancer in the left lung. In July, 1946, he coughed up "pus and blood" during a period of three weeks. In September, 1946, he began to have pains in the left hip and both shoulders. Around December, 1946, he noted a small, hard nodule in the left testicle. In January, 1947, multiple subcutaneous, hard, tender nodules appeared all over his body. In March, 1946, he began to lose weight and strength, the loss amounting to about 60 pounds in weight. His stools had been black off and on since April, 1946.

On admission to the hospital on Jan. 28, 1947, the patient appeared extremely ill and weak. Numerous subcutaneous tumor nodules were scattered over the entire body surface. There were flatness and absent breath sounds over the entire left lung. The heart was not enlarged. The rhythm was regular, the rate, 94 per minute. A systolic murmur was heard over the apex and pulmonic area. The blood pressure was 106/60. The liver was felt three fingerbreadths below the costal margin. A large, hard, firm tumor mass measuring 8.0 to 9.0 cm. in diameter was present in the left testicle. The scrotal skin presented a bluish discoloration. There was generalized adenopathy in the axillary, supraclavicular, and inguinal areas. Roentgen examination of the chest showed a homogeneous density occupying the entire left chest, displacement of the mediastinum toward the left side, and marked distention of the right lung. Bronchoscopy showed a tumor mass attached to the posteroinferior wall of the left primary bronchus about 2.0 cm. below the carina occluding the lumen. Histologic examination of tissue removed from this tumor showed only necrotic tissue. Histologic examination of one of the subcutaneous nodules showed an undifferentiated type of tumor resembling testicular tissue in appearance and cellular arrangement.

The temperature fluctuated between 98 and 99°F. with occasional rises up to 100° Fahrenheit. The heart rate varied between 84 and 110 per minute, occasionally rising to 120 per minute. The patient did not respond to symptomatic therapy; his debility gradually increased, and he died on Feb. 21, 1947.

Necropsy.—Numerous subcutaneous tumor nodules were scattered over the entire body surface. The left main bronchus was completely occluded by a tumor mass, and multiple abscesses were present in the left lower lobe. There was tumor invasion of the posterior mediastinum with necrosis and perforation of the esophagus and abscess formation in the mediastinum. A large tumor mass was attached to the left testicle. Tumor nodules of varying sizes were found in the adrenals, kidneys, walls of the small and large intestines, and retroperitoneal fat. The heart weighed 310 grams; the epicardial surface was covered by a shaggy fibrinous exudate and adhesions were present between the parietal and visceral layers of the pericardium. The pericardial cavity contained approximately 150 c.c. of cloudy, greenish fluid. A few grayish-pink, small tumor nodules were scattered through the wall of the left ventricle.

Histologic examination showed embryonal carcinoma with lymphoid stroma of the left testicle.

CASE 4.—A 54-year-old white man "bruised" a birthmark above the left ankle in 1942. The lesion was excised in 1943. Local recurrence and two small masses in the thigh along the course of the saphenous vein were removed in 1944. Excision of local recurrence, followed by skin graft, was performed in 1946. In October, 1946, a mass appeared beneath the graft. Biopsy of this mass at another hospital showed malignant melanoma, and amputation below the knee was performed on Oct. 31, 1946. In January, 1947, tender subcutaneous nodules appeared over the entire body, and the patient began to complain of continuous griping pains in the abdomen and of difficulty in getting his breath. He was admitted to the hospital on March 20.

Numerous subcutaneous tender nodular masses were found distributed over the entire body surface. The heart was not enlarged; the rhythm was regular and the rate, 88 per minute. No

murmurs were heard and the blood pressure was 148/96. There was diffuse tenderness on pressure over the abdomen; the liver was palpable, the edge being smooth. Roentgen examination of the chest showed nodular metastases in the left upper, left lower, and right lower lobes. The transverse diameter of the heart was 15.5 cm. and the intrathoracic diameter was 30 centimeters.

The patient was treated with methyl-bis (B-chloroethyl) amine hydrochloride; he was given 6.0 mg. intravenously (0.1 mg. per kilogram of body weight) every other day for four doses. However, he gradually became weaker and died on April 11, 1947. During the period of observation the temperature at first fluctuated between 98.6 and 101°F.; later the changes became wider and fluctuated between 97 and 102° Fahrenheit. The pulse rate varied between 72 and 110 per minute, rising occasionally to 120 coincidentally with the elevated temperature peaks.

Necropsy.—Subcutaneous nodular masses were found distributed throughout the entire body surface and nodular metastases were found in the lungs, heart, liver, adrenals, kidneys, gastrointestinal tract, and brain. The heart weighed 380 grams; isolated tumor nodules were found in the walls of both auricles, both ventricles, and interventricular septum, and one nodule was present at the base of the tricuspid valve. Microscopic examination showed malignant melanoma.

CASE 5.—A 60-year-old white man was admitted to the hospital on May 19, 1947. For the past fifteen to twenty years he had had a slight cough productive of small amounts of sputum. In 1942 he developed weakness, malaise, and easy fatigability. In 1945 his cough became worse; the sputum increased in amount and occasionally was streaked with blood. In the summer of 1946 radiologic examination of the chest showed tuberculosis in the left upper lobe and "some disease" in the right lung; the sputum, however, did not show tubercle bacilli. In September, 1946, the patient developed a constant pain in the right lower chest. In February, 1947, tuberculous lesions in both apices (positive sputum) and a solid tumor in the right lower lobe were found at another hospital where the right lower lobe was removed in March, 1947. Histologic examination was reported to show undifferentiated bronchogenic carcinoma and tuberculosis.

The patient was poorly nourished. There was a draining sinus in the right fifth intercostal space anteriorly. There were decreased expansion, flatness, and absent breath sounds over the lower one-half of the right chest. The heart was not enlarged; the rhythm was regular, the rate, 88 per minute. The sounds were of good tonal quality. The blood pressure was 126/82. Roentgen examination of the chest showed a fluid level in the right chest at the level of the second rib anteriorly, an area of irregular density in the upper part of the right lung field, and scattered areas of density in the upper one-third of the left lung.

Underwater drainage through the sinus in the right chest wall was instituted. Air was seen to escape during coughing, indicating a bronchopleural fistula. During bronchoscopy the bronchopleural fistula was seen through the stump of the open right lower lobe bronchus. Tissue removed from the orifice of the right upper lobe bronchus did not show tumor cells on histologic examination. On May 26 the patient developed a transient right hemiplegia. He gradually became weaker and died on June 21, 1947. The temperature fluctuated between 97 and 99°F. with occasional rises up to 100.2° Fahrenheit. The heart rate at first fluctuated between 80 and 90 per minute; during the last two weeks of the patient's life the rate varied between 90 and 100 per minute; occasionally it rose to 120 per minute coincidentally with the rises in the temperature. At no time was circulatory failure noted.

Necropsy.—The heart weighed 360 grams; grayish-white tumor nodules were present in the wall of the right auricle and interventricular septum varying from 1.2 to 2.5 cm. in diameter. The primary bronchus of the right lower lobe 7.0 cm. distal to the bifurcation of the trachea ended abruptly in a tumor mass measuring 10 cm. in diameter. Several multiloculated cavities filled with cheesy, gray material were present in the left upper lobe. Both adrenal glands were almost completely replaced by tumor; multiple tumor nodules of varying sizes were present in the lungs, both kidneys, small intestines, mesentery, lymph nodes, and the brain. The right pleural cavity contained several multiloculated encapsulated empyema cavities filled with thick, yellow, creamy pus. Histologic examination showed bronchogenic carcinoma, squamous type, and fibrocaseous tuberculosis.

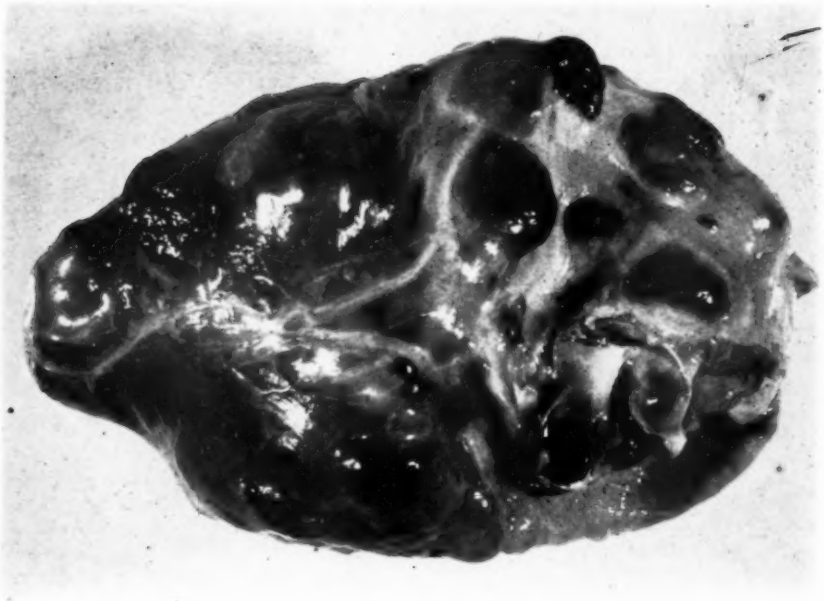


Fig. 4.—Case 6. External appearance of heart. Note the large, variously sized, darkly pigmented nodules.

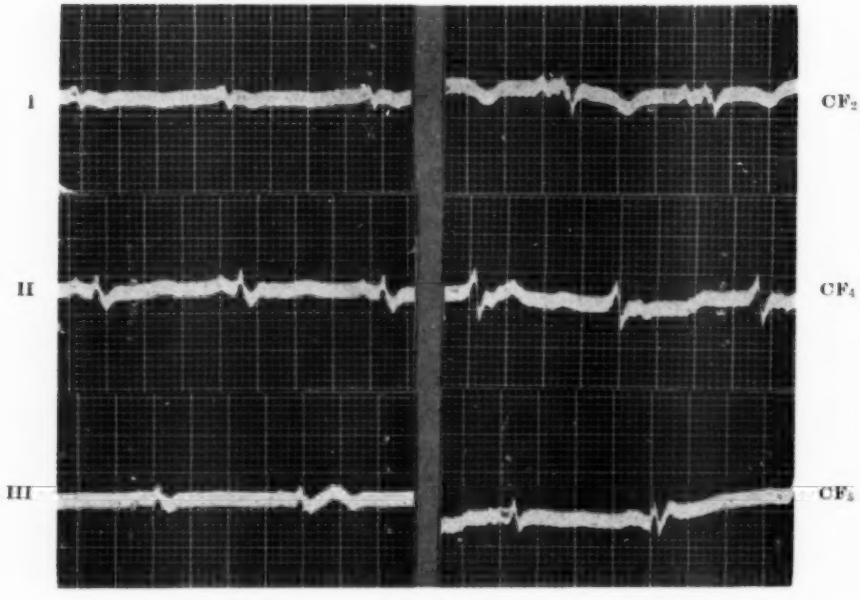


Fig. 5.—Case 6. Electrocardiogram. See text for description.

CASE 6.—A 55-year-old white man was admitted to the hospital on Sept. 18, 1946. In 1939 he began to have pain in the right eye. His doctor treated him for glaucoma. The pain subsided, but the patient lost vision in the right eye. In 1943 exophthalmos of the right eye was noted. Intermittent episodes of pain and swelling of the right eye then followed.

There was marked exophthalmos of the right eye; the bulbar and palpebral conjunctivae were markedly injected. A doughy, tender mass, about one inch long and one-half inch wide, was palpable temporally behind the lower lid; smaller but firmer masses were felt in both fornices which greatly limited movement of the eye. The pupil was small and fixed; the lens showed a cataract. The left eye was normal. The heart was not enlarged; the rhythm was regular, the rate, 72 per minute. No murmurs were audible. The blood pressure was 135/84. Roentgen examination of the chest revealed no abnormalities. The diagnosis of right intraorbital tumor was made and the right orbit was exenterated on Oct. 15, 1946. Histologic examination revealed malignant melanoma.

The patient gradually became cachectic. Subcutaneous nodules appeared all over his body and the liver became enlarged and nodular. Between July 10 and July 23, 1947, he received radiation therapy for palliation. This was of no avail and he died on July 24, 1947. The temperature was at normal levels with only occasional rises up to 100.6° Fahrenheit. The heart rate fluctuated between 72 and 110 per minute with an average rate of approximately 86 per minute. No murmurs were heard nor evidences of circulatory insufficiency noted. The electrocardiogram, taken about four hours before death, showed low voltage of all complexes in all leads, slurring of the QRS complexes in all leads, inversion of T waves, and depression of S-T in Leads CF_2 and CF_4 (Fig. 4).

Necropsy.—Numerous subcutaneous tumor nodules were found over the entire body surface. Discrete nodular metastases were present in the heart, pericardium, pleura, right lung, liver, spleen, pancreas, left adrenal, right kidney, renal pelves, ureters, urinary bladder, gastrointestinal tract, brain, and lymph nodes. The heart weighed 300 grams. Several large, bluish-gray tumor nodules were present in the pericardium, the myocardium of both auricles, the ventricles, and the interventricular septum. A large nodule measuring 4.0 cm. in diameter extended through the entire thickness of the interventricular septum.

The pertinent clinical and post-mortem data are summarized in Table I.

COMMENT

In Case 1 the extensive involvement of the heart muscle at necropsy was so extraordinary that the case aroused great interest. Clinically, during the patient's life no clue was found which indicated possible invasion of the heart by tumor. The only significant abnormal finding referable to the heart was the persistent tachycardia. This was thought to be secondary to the febrile course. The significance of enlargement of the heart as shown by x-ray examination was overlooked.

The varied and bizarre symptomatology and physical findings noted in the cases which have been reported are readily accounted for by the widespread metastases which in some instances involved almost every organ in the body. Of interest was the observation that metastatic involvement of the heart, which in some cases was so extensive that the major portion of the cardiac muscle was replaced by tumor, produced few or no symptoms directly referable to the heart. Similar observations have been made by previous investigators.[6-8] This explains the fact that so few instances of invasion of the cardiac muscle by tumor had been diagnosed ante mortem. In the rare instances the correct diagnosis was made because the tumor growth, either by its sheer size

TABLE I. SUMMARY OF SIGNIFICANT FINDINGS

CASE	RHYTHM AND RATE	ENLARGEMENT OF HEART	BLOOD PRESSURE	MURMURS	CARDIAC FAILURE	ECG	HEART WEIGHT (GM.)	EXTENT OF CARDIAC METASTASES	DIAGNOSIS
1	Regular 96-134	Moderate	108/64	Faint systolic at base	No	———	550	Extensive invasion of walls of all chambers	Malignant melanoma
2	Regular 80-116	No	120/76	None	No	———	260	Nodules in walls of both auricles and left ventricle	Malignant melanoma
3	Regular 84-120	No	106/60	Systolic at apex and at pulmonic area	No	———	310	Small nodules scattered through wall of left ventricle	Embryonal carcinoma of left testicle with lymphoid stroma
4	Regular 72-120	Slight	148/96	None	No	———	380	Nodules in walls of both auricles, ventricles and interventricular septum	Malignant melanoma
5	Regular 80-120	No	126/82	None	No	———	360	Nodules in wall of right auricle and interventricular septum	Bronchogenic carcinoma of right lobe bronchus
6	Regular 72-110	No	135/84	None	No	Low voltage of all complexes; slurring of QRS, inversion of T in CF_2 and CF_3	300	Nodules in walls of all chambers and interventricular septum	Malignant melanoma

or strategic location, produced bizarre and otherwise unexplainable symptoms and physical signs such as intense cyanosis, dyspnea, murmurs which varied in character and intensity with changes in body positions, intractable cardiac failure, arrhythmias, heart block, electrocardiographic abnormalities, unusual or irregular cardiac contour on radiologic examination, and sanguineous and recurring pericardial effusions.[8-10]

The six cases which form the basis of this report also were diagnosed only post mortem.

Analysis of the clinical findings in the cases reported in this communication and those reported in the literature, which are suitable for analysis, reveals the fact that the chief reason for failure to arrive at the correct diagnosis was the absence of any characteristic symptom or sign which would have called attention to the heart. In addition, it may be added, as Fishberg[10] has stated, that "in most of these, it is true, as little attention was devoted to the accurate study of the cardiovascular system as is usually accorded in patients suffering from advanced malignant disease." Tachycardia, otherwise unexplained, was the only constant abnormal finding. The electrocardiogram was likewise of no help. The abnormalities noted in the electrocardiograms[10,12] in most of the cases found in the literature consisted, as in one of the cases reported in this paper, of nonspecific changes such as low voltage complexes, depressed S-T interval, T-wave inversion, and various forms of heart block.

On the basis of these findings one is justified in stating that cardiac metastasis should be thought of in any patient who has malignant disease elsewhere in the body if tachycardia of unexplained origin is present, even if there are no other signs or symptoms which would indicate invasion of the heart. If, in addition, one or more of the abnormal cardiac signs and symptoms which we have listed develop, the diagnosis of metastatic invasion of the heart can be made with reasonable certainty.

SUMMARY

1. A case of extraordinary metastatic invasion of the heart secondary to malignant melanoma is reported. In addition, five other instances of cardiac invasion by metastatic tumor growth are briefly described.

2. The only constant abnormal physical finding noted referable to the heart during life was a persistent tachycardia which was otherwise unexplained.

3. It is believed that the diagnosis of metastatic invasion of the heart by neoplasm can be made with reasonable certainty if an otherwise unexplained persistent tachycardia is present in a patient suffering from malignant disease elsewhere in the body.

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SUPERNORMAL PHASE OF INTRAVENTRICULAR CONDUCTION

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THE law of rest and recovery governs the property of conduction in the heart and explains most of its disturbances. Thus, in cold-blooded and in mammalian hearts, the conduction time is optimal after a longer pause and becomes prolonged if the recovery time is shortened. Occasionally exceptions to this rule have been observed. One such exception is that the second impulse in a series of regularly conducted impulses appearing after a long pause exhibits an abnormal conduction pattern. The explanation offered is that the first impulse appearing after a longer pause is followed by a particularly prolonged refractory period so that the subsequent impulse finds the conduction tissue in a less favorable state of recovery.[10]

Another explanation for exceptions to the rule which has just been stated utilizes the concept of the supernormal phase of recovery. Originally found in nerve and muscle fibers,[2] it was also observed in the heart under certain conditions.[1,3] This supernormal phase of excitability and contractility which follows the relative refractory phase seems to exist in a very slight degree in normal nerve and muscle tissues, but is markedly pronounced in excised nerve and muscle fibers under abnormal conditions. Many observations show that the supernormal phase is closely related to and coincides with the phase of the negative after-potential.

A series of clinical observations was published in which abnormalities of conduction were interpreted as being due to the supernormal phase. Obviously no tests with threshhold stimuli were possible in man; therefore, the evidence is based solely on the interpretation of unusual tracings.[6-9,11] Such tracings were rather rare and always concerned auriculoventricular conduction. Some of the published cases of a supernormal phase of conduction in partial auriculoventricular block were interpreted as being due to the interference between automatic and conducted beats. Therefore, the description of an unusual electrocardiogram which can be explained by the existence of a supernormal phase of *intra*ventricular conduction seems fully warranted.

OBSERVATION

A 56-year-old, very obese woman was hospitalized for painful swelling of the wrists, the small joints of both hands, and the right knee. A similar episode

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of joint swellings had occurred ten years previously. The present complaints were of two weeks' duration.

Examination revealed the involved joints to be red, swollen, and tender. Both ankles showed slight pitting edema. The blood pressure was 180/110. The temperature was 102° Fahrenheit. Clinical examination of the heart disclosed a moderate enlargement of the left ventricle and soft systolic murmurs over the apex and aorta. Moist râles were present in both lung bases. Possibly as a result of the obesity, the liver edge could not be palpated. Roentgen examination revealed enlargement of the left ventricle, a normal aorta, and evidence of pulmonary congestion.

Laboratory studies showed moderate albuminuria without other disturbance of kidney function. A slight glycosuria appeared for a few days. The blood sugar was 150 mg. per cent but soon fell to 89 mg. per cent and remained at approximately this level. The blood count showed 15,000 leucocytes and normal differential and erythrocyte counts. During the first week the erythrocyte sedimentation rate varied between 116 and 126 mm. in one hour, thereafter, gradually becoming normal.

A provisional diagnosis was made of acute rheumatic fever with hypertension of unknown origin and mild diabetes mellitus. There was no evidence of a mitral valvular lesion of rheumatic etiology. Under salicylate therapy the joint changes disappeared within two weeks. The patient also received digitalis in a dose of 0.3 Gm. daily until she developed a 2:1 A-V heart block. The pulmonary congestion rapidly disappeared. The patient was discharged as improved.

The electrocardiogram taken on admission (Fig. 1, *A*) exhibits a left axis deviation, a rate of 82 per minute, and a P-R interval of 0.18 second. The high R wave and short S wave in the chest lead over the left ventricle are suggestive of left ventricular hypertrophy. Fig. 1, *B* was obtained nineteen days later when the patient was markedly improved. It reveals the pattern of left bundle branch block. The P-R interval is prolonged to 0.24 second and the rate is increased to 94 per minute. Chest lead CR_4 does not show the expected delay of the appearance of the intrinsic wave over the left ventricle. This may be due to the fact that the electrode in this instance was still over the right ventricle.

Nine days later a 2:1 A-V block was registered in addition to the bundle branch block. The P-R interval of the conducted beats was still 0.24 second. At this time the dose of digitalis had been reduced from 0.3 to 0.2 Gm. daily. Eight days later the tracing shown in Fig. 2 was obtained and will be described in detail presently. On the next day and during the following two weeks a sinus rhythm with left axis deviation was registered with marked digitalis effect on the RS-T segment and T wave visible in all leads. There was no bundle branch block and no A-V heart block.

Fig. 2 shows the electrocardiogram which is of most interest. The basic auricular rhythm is a sinus rhythm with a rate of approximately 68 per minute. An auriculoventricular conduction disturbance exists in which the P-R interval becomes increasingly prolonged until every fourth to eighth ventricular beat is dropped. We are, therefore, dealing with Wenckebach periods, which are com-

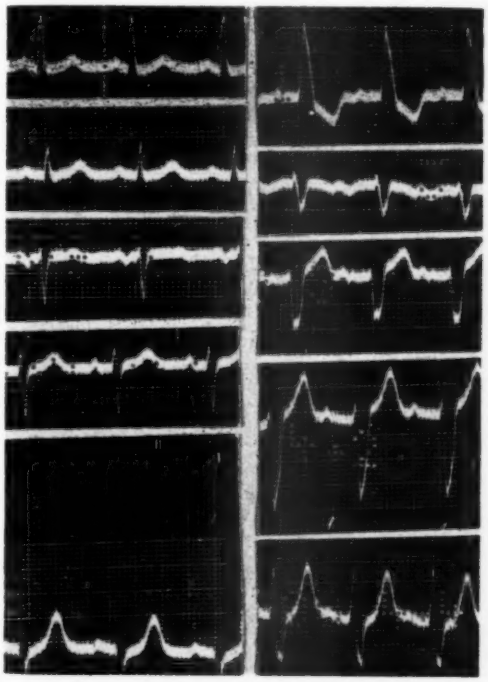

Fig. 1.—*A*, Left axis deviation. *B*, Left bundle branch block.

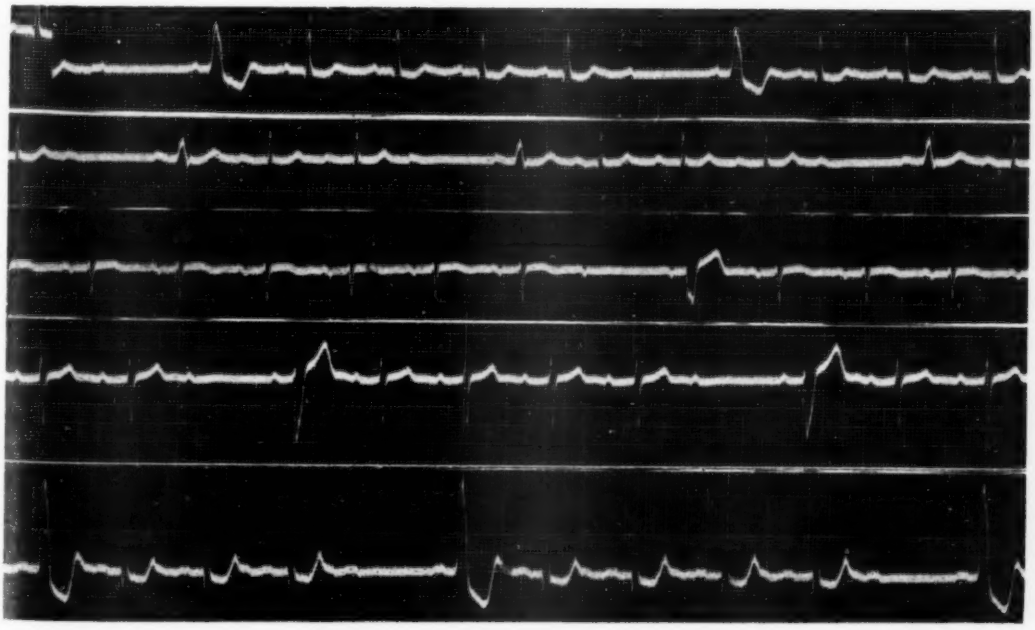

Fig. 2.—Wenckebach's periods and abnormal intraventricular conduction.

monly seen when 2:1 A-V block reverts to a normal sinus rhythm. The RS-T segments show clearly the effect of the digitalis because they are depressed in a characteristic way, particularly in Leads I and CR_4. Unusual, however, is the QRS complex of the first conducted beat after a blocked P wave because it shows the pattern seen during the sinus rhythm and bundle branch block in Fig. 1,*B*. In our opinion, there can be no doubt about the identity of these QRS complexes in the two tracings. The finest slurring and notching are minutely duplicated. Only in the apical chest lead do differences exist, but these are not uncommon because of the fact that in obese patients with a high diaphragm the electrode is very often not placed far enough to the left to be situated over the left ventricle. Note that all complexes, with the exception of the first one after the pause, resemble each other closely.

The P-P, R-R, and P-R intervals in all leads of the tracings from which Fig. 2 was obtained were carefully measured and the data obtained are reproduced in Table I. The auricular rate is seen to vary slightly with a tendency to be slower for one or two cycles following a dropped beat. The R-R intervals during the periods of conduction reveal the same variations as the P-P intervals; the abnormal beats follow the preceding QRS complex after a time which varies between 1.62 and 1.75 seconds. The P-R interval increased markedly from the first to the second conducted beats and increases only slightly just before the dropped beat. The P waves precede the abnormal beats with the fairly constant interval of 0.21 to 0.23 second.

DISCUSSION

The abnormal ventricular complexes appearing in Fig. 2 after the long pause may represent idioventricular beats originating in a ventricular center. This is not a rare phenomenon in tracings with partial A-V heart block. In our opinion, however, the abnormal beats are conducted from the auricle and are not automatic idioventricular beats. This conclusion is based mainly on two facts.

1. The abnormal beats appear to be similar in all details to those observed during the regular sinus rhythm with bundle branch block (Fig. 1,*B*). There is only the slight difference in Lead CR_4 which was discussed. All the details, including notching and slurring of the QRS complexes in the other leads, are the same in the QRS complexes of Fig. 1,*B* and in the abnormal QRS complexes of Fig. 2.

2. The length of the periods before the abnormal complexes in Fig. 2 varies, while the P-R interval of the abnormal beats is fairly constant. If the abnormal QRS complexes were idioventricular beats independent of auricular stimuli, a greater variation of the P-R intervals would be expected.

The conclusion that we are dealing with conducted beats justifies the diagnosis of intermittent bundle branch block. In intermittent bundle branch block with dropped beats, however, the block usually disappears after a longer pause because of the better recovery of the bundle branch involved; if sinus rhythm

TABLE I. AURICULAR AND VENTRICULAR INTERVALS AND AURICULOVENTRICULAR CONDUCTION TIME IN FIVE LEADS

LEAD I			LEAD II			LEAD III			LEAD CR_2			LEAD CR_4		
P-P	R-R	P-R	P-P	R-R	P-R	P-P	R-R	P-R	P-P	R-R	P-R	P-P	R-R	P-R
86	175	22	85	162	32	88	90	26	87	89	27	88	168	30
90	94	26	87	88		88	90	28	87	169	29	88	90	23
86	90	28	83	86	23	88	87	28	86	90	23	86	84	26
88	88	28	84	166	26	86	87	28	85	86	27	85	88	26
86	88	29	85	84	31	88	90	28	86	89	27	86	168	28
85	173	22	86	86	23	84	172	28	86	88	28	84	86	22
88	88	24	82	86	26	92	92	23	88	169	30	92	87	24
92	87	24	86	165	26	88	86	26	88	89	23	84	88	28
84	87	26	82	89	28	88	84	28	88	88	26	86	89	28
84	94	28	84	86	22	82	84	28	88	87	26	86	166	29
88	164	23	88		25	82		28	88	88	27	88	92	22
82	85	24	83		27				87	87	27	84	88	25
84	86	26	84						88		27	90	88	26
86	170	21										88	174	30
84	88	26										86	88	22
84	86	26										86	89	24
80												88		26
92												88		
84												86		
88												88		

Figures represent sec. 100.

without irregularity prevails, bundle branch block appears quite irregularly. In Fig. 2 we find the paradoxic phenomenon of bundle branch block appearing only after the longer pause.

For the explanation of this finding, the supernormal phase of excitation seems to be the most logical. The first impulse arriving at a damaged area of the left bundle branch is unable to traverse it in time to activate the left ventricle directly. An impulse reaches the left ventricle later by way of the septum and over muscular pathways from the right ventricle. This impulse leaves the damaged area in a hyperexcitable state, and if the next stimulus arrives during this state of supernormal excitability, the conduction is so much improved that normal ventricular complexes appear.

The question arises as to whether the supernormal phase can last long enough after every beat to explain the normal conduction of the series of ventricular complexes following the abnormal one. We know that the excitation wave reaches the auriculoventricular node 0.04 to 0.05 second after the beginning of the P wave and is conducted in the bundle branches about 0.05 to 0.06 second later. Therefore, the distance from the beginning of the abnormal QRS complex to the beginning of the following P wave will indicate approximately the moment of conduction in the bundle branch. This time measures in Fig. 2 (Lead I) in the successive cycles: 0.68, 0.62, 0.64, 0.60, 0.64, 0.64, 0.60, 0.59, 0.60, 0.60, 0.60, 0.60 second; that is, it varies between 0.59 and 0.68 second. In Table II is compiled the duration of the supernormal phase after the transmission of an impulse in nerve, in the turtle heart and in the human heart, as reported in the literature. In investigations of the supernormal phase in auriculoventricular block, the duration of the former is usually measured from the beginning of the R wave

TABLE II. DURATION OF SUPERNORMAL PHASE

AUTHORS	DURATION OF SUPERNORMAL PHASE FOLLOWING PRECEDING SYSTOLE (SEC.)	OBJECT
Adrian and Lucas[2]	0.01–0.04	nerve fiber
Ashman[3]	3.00–4.00	turtle heart
Ashman and Herrmann[4]	0.31–0.795 0.09–0.30	human heart human heart
Lewis and Masters[8]	0.425–0.708	human heart
Wolferth[12]	0.45–0.74	human heart
Scherf and Schott[11]	0.10–0.16 0.22–0.28	human heart human heart
Kline and associates[7]	0.6–1.04	human heart
Luten and Pope[9]	0.59–0.64	human heart
Jervell[6]	0.50–0.55	human heart

to the following P wave of an abnormally well-conducted impulse. The table shows that some of the figures obtained in nine different human hearts are well within the range found in our patient.

A case showing many similarities to that described in this paper has been reported previously.[3] The patient was a 19-year-old man who had a history of two attacks of rheumatic fever, and who was admitted during the active phase of a third attack. He had also received digitalis, as had our patient. The electrocardiograms revealed a sinus tachycardia with a rate between 110 and 120 beats per minute. Periodically, dropped beats appeared and the first conducted beat after the blocked P wave showed widening and slurring of the QRS complex similar to that seen in our patient. In discussing the interpretation of this observation Von Hoesslin concluded that the best explanation was an escape of a deep idioventricular center. The same arguments used in our case may be considered valid in rejection of this interpretation. In another interesting case[4] showing features speaking for the existence of a supernormal phase, idioventricular beats appeared which, in the opinion of the authors, originated above the bifurcation of the auriculoventricular conduction system. The longer the rest interval of the preautomatic pause, the wider was the QRS complex of these beats and the slower the intraventricular conduction. The possibility of a supernormal phase, as accepted in our case, was rejected, and the authors believed that the increased intraventricular pressure, following a longer intraventricular block, delays conduction through "pressure block." In our case, this explanation seems improbable since the form of the QRS complexes is constant in spite of variation in the length of the preceding pauses and because of the similarity between the QRS complexes during the bundle branch block (Fig. 1,*B*) and during the abnormal phenomenon. No other forms of the QRS complex were seen in our case but the two shown in Figs. 1 and 2.

The supernormal phase in healthy muscle or nerve tissue is very short and often cannot be demonstrated. It is more readily demonstrable and is markedly prolonged if some tissue damage is present. There is no doubt that myocardial damage existed in the case discussed in this paper. It is difficult to ascertain the nature of this damage. The elevation of the systolic and diastolic blood pressure and the enlargement of the left ventricle in a 56-year-old patient with obesity and mild diabetes make myocardial damage due to coronary sclerosis possible. The evidence of acute polyarthritis with an increased sedimentation rate, leucocytosis, and fever suggests the possibility of myocardial damage caused by an active rheumatic carditis. The fact that abnormal electrocardiograms appeared during a phase when the clinical signs began to improve does not militate against this diagnosis.

In this case, as well as in the case presented by Von Hoesslin, digitalis had been administered. The role that this drug played in the production of the described phenomenon is uncertain, but it may very well have been partly or entirely responsible.

SUMMARY

A case of abnormal intraventricular conduction is reported, which is interpreted as being due to the phenomenon of a supernormal phase of conductivity.

Our thanks are due to Dr. Milton J. Raisbeck for the permission to publish the electrocardiographic tracings.

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Abstracts and Reviews

Selected Abstracts

Mussafia, A.: Electrocardiographic and Clinical Studies on Certain Types of Myocardial Infarction: Supra-apical, Endocardial, Epicardial, Lateral and Anterolateral Infarction. Arch. d. mal. du coeur. 40:369 (Sept.), 1947.

The article presents a classification of myocardial infarcts after a study of 200 instances of infarction observed over a ten-year period. The results were based on standard leads and chest Leads CR_2, IVR, and occasionally on Leads CR_5 and CR_6. Anteroapical infarcts were observed in forty-five cases (22.5 per cent) and posterobasal infarcts in forty-six examples (23 per cent). Supra-apical infarcts (the anteroseptal infarct of Wilson) were present twenty-seven times (13.5 per cent), endocardial infarcts seven times (3.5 per cent), epicardial infarcts nine times (4.5 per cent), lateral infarcts (Type $Q_1T_1CR_5$) five times (2.5 per cent), and anterolateral infarcts (Type $Q_1T_1CR_4CR_5$) four times (2 per cent). "Atypical" infarcts (not discussed) were noted in fifty-seven instances (28.5 per cent). Pathologic confirmation of the electrocardiographic pattern was obtained in twelve cases.

HECHT.

Biorck, G.: Ergotamine and Apparent Coronary Insufficiency. Brit. Heart J. 9:181 (Oct.), 1947.

The author believes that the Levy hypoxemia test not only discloses latent coronary artery disease but that it also produces apparently pathologic electrocardiograms in patients with symptoms of cardiac neurosis in the absence of organic changes in the coronary circulation.

This impression led the author to try to counteract nervous factors which may be present. Blocking of the sympathetic nerves was regarded as one possible way of studying the problem of the importance of functional factors in some cases of unexpected positive hypoxemia tests. Ten neurotic patients without evidence of organic heart disease were studied. The hypoxemia test was performed with 9 per cent oxygen in nitrogen for ten minutes and evaluated according to the criteria of Levy. A few days to one month later, the ergotamine-hypoxemia test was performed as follows: After a previous electrocardiogram taken at rest, the patient was given ergotamine 0.5 mg. intramuscularly or subcutaneously. After twenty minutes an electrocardiogram was taken again. The hypoxemia test was then started. After ten minutes a third electrocardiogram was taken and the patient was permitted to inhale 100 per cent oxygen. Nine of ten positive hypoxemia tests became negative after the administration of ergotamine. This indicates that some factors which contribute to positive hypoxemia tests can be abolished by ergotamine. Further investigations are needed to elucidate this and other mechanisms responsible for positive hypoxemia tests.

SOLOFF.

Parkinson, J., and Papp, C.: Repetitive Paroxysmal Tachycardia. Brit. Heart J. 9:241 (Oct.), 1947.

Repetitive paroxysmal tachycardia is defined as recurring short runs of auricular, nodal, or ventricular extrasystoles. Such runs or paroxysms of tachycardia are almost constantly present for months or for years and only occasionally are interrupted by periods of normal sinus rhythm.

The authors have collected forty cases. The ages of the patients varied from 4 to 75 years. The auricular form was more common in patients under 40 years. Auricular flutter and fibrillation were more common in adults. The longest paroxysmal state was ten years.

The symptoms consisted of: (1) palpitation, independent of exertion, (2) occasional breathlessness, and (3) in six, syncopal attacks. Organic heart disease was present in three patients only.

The electrocardiographic features consisted of: (1) repetitive auricular paroxysmal tachycardia, twenty-four cases; (2) repetitive auricular flutter, four cases and repetitive auricular fibrillation, one case; (3) repetitive nodal tachycardia, two cases; and (4) repetitive ventricular tachycardia, nine cases.

The nature of this condition is unknown. It appears to be a connecting link between extrasystoles and ordinary paroxysmal tachycardia. It may be the result of a congenital peculiarity in the conducting system. The prognosis is good; children tend to grow out of it in adolescence. In adults also it tends to subside. Treatment is usually of no value. Quinidine may be tried but is usually ineffective.

SOLOFF.

Cossio, P., Dambrosi, R. G., and Warnford-Thomson, H. F.: The First Heart Sound in Auricular and Ventricular Extrasystoles. Brit. Heart J. 9:275 (Oct.), 1947.

This study deals with the causes for the variation in intensity of the first sound of a premature beat. Thirty patients with extrasystoles were studied by means of simultaneous electrocardiographic and phonocardiographic records. Sixteen patients had auricular and fourteen, ventricular extrasystoles.

Auricular Extrasystoles.—In all but one subject, the extrasystolic first sound was louder than the first sound of the preceding and the following normal beats. The interval between the onset of QRS and the reinforced first sound varied from 0.05 to 0.08 second, while in the normal beats or premature beats without reinforcement of the first sound, it was 0.03 to 0.05 second. The greatest intensity and delay of the first heart sound occurred when the extrasystolic ventricular systole was in mid-diastole, whereas the less intense sounds occurred when the extrasystolic ventricular systole was in early or very late diastole.

Ventricular Extrasystoles.—The extrasystolic first sound was louder than the normal first sound in nine, of equal intensity in one, of equal or less intensity in one, and of less intensity in three. The interval between the onset of QRS and the increased ventricular extrasystolic first sound was from 0.08 to 0.12 second, while in normal beats it was 0.03 to 0.06 second. Diminished extrasystolic first sounds occurred whenever the premature ventricular systole coincided with the descending limb of the T wave of the preceding cycle or fell just in front of the next P wave of sinus origin. Increased extrasystolic first sounds occurred whenever the premature ventricular systole fell just after the T wave or just after the normal P wave. In four of fourteen cases a split first sound was recorded in the premature beats.

The authors suggest the following explanation for these findings: Normally, the onset of a normal ventricular contraction finds the A-V valves in the position of almost complete closure. With premature contraction, the A-V valves are at a lower position; more time must elapse before their closure, and their movement and, consequently, their vibration is increased. When the onset of premature ventricular extrasystole coincides with auricular systole of sinus origin or when a premature systole falls at the end of or immediately after the phase of rapid inflow, the first sound is intensified and delayed; when it falls before the end of the phase rapid inflow, because of incomplete ventricular filling, the valves are insufficiently stretched to intensify the first sound. The asynchronous contraction of the ventricles in premature ventricular contraction is the cause for the splitting of the first sound. The asynchronous closure of mitral and tricuspid valves also explains why ventricular extrasystoles have a lower incidence of intensified first sound than auricular extrasystoles.

SOLOFF.

Benn, J.: The Prognosis of Patent Ductus Arteriosus. Brit. Heart J. **9**:283 (Oct.), 1947.

Benn states that it is important to assess the increased risk that the presence of a patent ductus involves because surgical intervention to correct it is becoming so frequent that some surgeons recommend operation in all uncomplicated cases between the ages of 7 and 10 years. Previous studies on the prognosis are unsatisfactory because no distinction is made between those who had symptoms and those who did not.

Forty-six cases were collected and divided into two groups. Group A, consisting of thirty cases, was collected from a school cardiac clinic in Bristol, save for one woman, 23 years of age, who was referred from an antenatal clinic. This group approximates a good sample of the condition since it probably represents almost every type of case observed in the younger people in Bristol. Group B, consisting of sixteen cases, was collected from areas outside Bristol. The patients composing this group were referred often because of symptoms. Group B approximates more nearly the type of case generally reported. The patients of these two groups were followed for a period of eight years.

Six of Group A and two of twelve surviving members of Group B had symptoms such as breathlessness on exertion, fatigue, cyanosis on occasion, and frequent colds. Five of Group B had bacterial endocarditis and only one, who was cured by penicillin, is alive now.

In two cases the classical murmur had disappeared without other evidence that the ductus had closed. Both the murmur and thrill may vanish with increasing age.

Of forty patients with electrocardiographic tracings, one had left axis deviation and one had right axis deviation; the remaining thirty-eight had no axis deviation. Of fifteen with x-ray studies, all had prominent pulmonary arteries. Eight of twenty patients in Group A and seven of ten in Group B were regarded as having pulmonary congestion on the basis of the appearance of the hilar shadows. Fifteen of seventeen of Group A with weights available were below normal weight. This was especially true for female patients. The female subjects were taller than normal.

No patients in Group A died or developed bacterial endocarditis or heart failure. In Group B, four patients died of bacterial endocarditis and one recovered from this disease.

The author believes that the indications for surgery should be (1) bacterial endocarditis, (2) recovered bacterial endocarditis, (3) cardiac embarrassment, and (4) poor physique.

SOLOFF.

Wiggers, C. J., Levy, M. N., and Graham, G.: Regional Intrathoracic Pressures and Their Bearing on Calculation of Effective Venous Pressures. Am. J. Physiol. **151**:1 (Nov.), 1947.

Intrathoracic pressures were recorded by optical capsules from eight different regions around the canine heart. Only minimal quantities of air were introduced into the mechanically created pockets. It was demonstrated that pressure obtained from pockets of the right lower thoracic cavity are little influenced by variations in pressures induced by cardiac movements but are otherwise similar to those derived from regions adjacent to the heart and that they change directionally with them. Pressures obtained from this region may be used in calculating trends of effective venous pressures.

HECHT.

Gregg, D. E., and Shipley, R. E.: Studies of the Venous Drainage of the Heart. Am. J. Physiol. **151**:13 (Nov.), 1947.

Coronary inflow and venous drainage were measured in fifty dogs by open chest experiments employing visual and optical recording rotameters and an orifice meter (Am. J. Physiol. **142**:44, 1944). With this technique it was found that almost all of the coronary sinus flow arose from the left coronary artery, although only about three-fourths of the flow of the left coronary artery drains by this route. Venous blood of the right heart drains through the anterior cardiac veins.

Acute occlusion of the coronary sinus causes congestion of the left heart, elevates the pressure in the sinus and in the great cardiac veins, increases the flow through the anterior cardiac

veins, and causes little if any reduction in coronary venous inflow. This suggests that the anterior cardiac veins may serve as alternate routes of drainage for the left ventricle. A somewhat similar response (rerouting of run-off with unaltered inflow) is obtained when the anterior coronary veins are ligated. If all visible venous channels are ligated, drainage still occurs, suggesting the presence of extensive collateral drainage channels. In experiments where an attempt was made to ligate all but the Thebesian veins, the ventricles became markedly hemorrhagic except for portions of the inner third of the left ventricle and the septum. It was demonstrated, however, at post-mortem examination that a few veins, possibly serving those regions, had remained unoccluded.

Chronic occlusion resulted in sizable anastomoses between the superficial veins of the heart and the extracardiac veins. It appears from these experiments that the Thebesian vessels play only a limited role in coronary drainage.

HECHT.

LeVeen, H. H., and Fishman, W. H.: Combination of Evans Blue With Plasma Protein: Its Significance in Capillary Permeability Studies, Blood Dye Disappearance Curves, and Its Use as a Protein Tag. Am. J. Physiol. **151**:26 (Nov.), 1947.

In man, the percentage of disappearance of Evans blue dye from the plasma varies widely over a twenty-four hour period (approximately 50 per cent) and is far in excess of the albumin turnover. When injected in large amounts, dye may appear in the pancreatic juice (one dog). In vitro experiments demonstrate that T-1824 combines with purified albumin, but also, to a lesser extent, with all globulin fractions. Activated resins remove 50 per cent of the dye from an albumin-dye mixture, suggesting that dissociation of the dye-albumin complex may readily occur. Un-ionized dye molecules may occasionally diffuse past capillary membranes and be fixed by tissue protein (staining) or secreted ("trapped") in ionized form. Tissue staining may in part account for the rapid early disappearance phase upon injection of dye into the blood stream. The rapid turnover of T-1824 and the ready dissociation of the dye-protein complex precludes the use of Evans blue as a tag for protein in metabolic studies.

HECHT.

Root, W. S., Walcott, W. W., and Gregerson, M. I.: Effects of Muscle Trauma and of Hemorrhage Upon the Cardiac Output of the Dog. Am. J. Physiol. **151**:34 (Nov.), 1947.

Shock ensues when the blood volume of dogs is reduced by 30 to 40 per cent following muscle trauma. The cardiac output in fourteen dogs, as determined by the Fick method, was found to be reduced to only 10 to 25 per cent of the control values, with exceedingly small outputs per beat (1 to 3 ml.). Calculated peripheral resistance increased one- to fivefold over the control values. The changes are less pronounced in dogs that did not develop shock following the trauma. Similarly, cardiac output decreased immediately following hemorrhage in twelve dogs bled 10 to 50 per cent of their control blood volumes. In this group, blood pressure changes were more pronounced and increases in peripheral resistance less striking than in the traumatized animals.

HECHT.

Miller, A. T.: Excretion of the Blue Dye, T-1824, in the Bile. Am. J. Physiol. **151**:229 (Nov.), 1947.

Ligating the cystic duct of nine dogs allowed the collection of hepatic bile before, during, and following the administration of Evans blue. Dye appeared in the bile thirty minutes after injection into the blood stream and reached a maximum concentration within the second hour. Bile accounted for only 2 to 7 per cent of the dye leaving the blood stream during that interval. The dye concentration in the bile appears to be independent of bile flow and is usually less than one-half the plasma dye concentration.

HECHT.

Miller, A. T.: A Re-evaluation of the T-1824 Mixing Curve. Am. J. Physiol. **151**:234 (Nov.), 1947.

The true disappearance slope of the Evans blue dye from plasma is preceded by mixing of the dye in the plasma. This may be divided into a rapid phase (Phase I), interpreted as demonstrating mixing of freely circulating plasma, and into a slower phase (Phase II) reflecting diffusion of dye into noncirculating plasma. In dogs, the first phase appears to be completed in four to six minutes, the second in thirty to fifty minutes. Extrapolation of Phase II of the mixing curve permits calculation of circulating plasma, while extrapolation of the true disappearance curve provides an index of total plasma volume. In 105 experiments on twenty-four dogs, the average circulating plasma volume was 86 per cent of the total plasma volume.

Cruickshank and Whitfield's conclusions that the extrapolation of Phase I of the mixing curve represents the true plasma volume are again challenged.

HECHT.

White, H. L., Heinbecker, P., and Rolf, D.: Endocrine Influences on Cardiac Output and Oxygen Consumption in Dogs. Am. J. Physiol. **151**:239 (Dec.), 1947.

Thyroidectomy and hypophysectomy produce prompt and permanent falls in oxygen consumption and in cardiac output in normal dogs as measured by the Fick principle. Administration of anterior pituitary hormone (Preloban) increases oxygen consumption and restores cardiac output in the hypophysectomized animal and also, to some extent, in the thyroidectomized animal. Preloban increases cardiac output in the normal dog. Denervation of the neurohypophysis does not alter cardiac output and oxygen consumption. These findings parallel previously observed changes in renal blood flow produced by the same procedures. It is postulated that the anterior lobe of the pituitary gland produces a substance which brings about increase in oxygen consumption, in cardiac output, and in renal flow. The observed effects cannot be explained by the action of thyrotropic or adrenocorticotropic hormones.

HECHT.

Lawson, H. C., Overbey, D. T., Moore, J. C., and Shadle, O. W.: Mixing of Cells, Plasma and Dye T-1824 in the Cardiovascular System of Barbitalized Dogs. Am. J. Physiol. **151**:282 (Dec.), 1947.

The circulatory mixing of cells, plasma, and dye solutions was studied in barbitalized and splenectomized dogs. It appears that complete mixing is accomplished in from three to five minutes when mixing times are determined by arterial hematocrit determinations and optical densities of dyed plasma. Continued rapid disappearance of injected dye beyond the first five minutes is ascribed to escape of dye from the vascular compartment.

HECHT.

Overbey, D. T., Moore, J. C., Shadle, O. W. and Lawson, H. C.: Rate of Disappearance of Dye T-1824 From Arterial Blood. Am. J. Physiol. **151**:290 (Dec.), 1947.

Full logarithmic plotting of dye disappearance curves demonstrates a relationship between dye concentration and time that is expressed $C_t = \frac{C_1}{T_P}$ where C is the dye concentration at time t, C_1 is the concentration at one minute; T, the time of injection in minutes; and p, a fractional power (0.0554). A truly exponential rate of dye disappearance is achieved only after two to four hours and three phases of dye disappearance are recognized: an initial rapid disappearance phase (one hour), an intermediate phase (one to three hours), and finally after three hours, a truly exponential phase. Any injection of dye into a previously dye-injected animal must pass through all three phases. A first and a second injection of dye behave identically when allowance is made for the changing rate of disappearance in time. (This is at variance with the reports of Cruickshank and Whitfield.)

HECHT.

Grollman, A.: Effect of Pregnancy on the Course of Experimental Hypertension. Am. J. Physiol. **151**:373 (Dec.), 1947.

Hypertension was induced in rats, rabbits, and dogs by application of a constricting figure-of-eight band to both kidneys or to one kidney with removal of the other. A tendency for the blood pressure to decline during pregnancy was noted in all experiments. The response decreased with increasing size of the species. Pseudopregnancy, induced in the rat by stimulation of the cervix and in the rabbit by mating with sterile partners, and occurring spontaneously in dogs following estrus, did not alter the blood pressure of the hypertensive animals. The reduction in blood pressure is considered to be primarily the result of the increased size of the vascular bed induced by the presence of the placenta. There were no symptoms suggestive of eclampsia and there was no tendency to abortion or fetal death among the hypertensive animals.

HECHT.

Morse, M., Cassels, D. E. and Schlutz, F. W.: Available and Interstitial Fluid Volumes of Normal Children. Am. J. Physiol. **151**:438 (Dec.), 1947.

Simultaneous determinations of plasma volume and thiocyanate space, following the method of Gregerson and Stewart, were performed on sixty-five children varying in age from 3 to 17 years. The data are correlated statistically for age, height, weight, surface area, height and weight, height and index of build, height and chest girth, and weight and index of weight. The average available fluid volume measured 287 ml. per kilogram of body weight. Surface area was found to be the best standard of reference. The fluid volume did not vary with the state of nutrition and remained relatively constant throughout the age range studied when related to unit of body weight. From available data it appears that the available fluid volume for the child and adolescent exceeds that of the adult when expressed in milliliters per kilogram of body weight.

HECHT.

Nichol, A. D. and Brannan, D. D.: The Differentiation of Patent Ductus Arteriosus and Atrial Septal Defect. Am. J. Roentgenol. **58**:697 (Dec.), 1947.

In patent ductus arteriosus, blood from the aorta is shunted into the pulmonary artery. The artery dilates to accommodate the increased blood volume, which on returning to heart results in enlargement of the left atrium. The increased filling of the left atrium and left ventricle increases the systolic output delivered to the aorta. Roentgenographically, these facts are manifest by the unusual combination of slight left atrial enlargement, definite left ventricular enlargement, and definite enlargement of the pulmonary artery and the first and second portions of the aorta. Clinically, there is usually no cyanosis, usually typical murmurs, localized pulsations in the second left intercostal space, a high systolic and low diastolic blood pressure, a normal electrocardiogram or left axis deviation, and slight circulatory insufficiency.

In atrial septal defect, the right atrium receives the peripheral venous flow and in numerous instances, a large complement of blood from the left atrium. This increased volume of blood causes enlargement of the right atrium and right ventricle; it also increases the right ventricular systolic output which results in considerable enlargement of the entire pulmonary vascular system. When this increased blood volume is returned to the left side of the heart, the septal defect shunts part of the blood from the left to the right atrium. This prevents an otherwise extreme enlargement of the left atrium and also results in decreased left ventricular filling, which, in turn, results in decreased left ventricular output and decreased peripheral blood flow. These changes are manifest roentgenographically by an increase in heart size due to marked increase in the size of the right atrium and right ventricle, associated with dilatation of the pulmonary artery and its branches. In contrast, the aortic knob is small and inconspicuous. Clinically, there is a variability of murmurs and thrills; right axis deviation and abnormal P waves in the electrocardiogram, which may also show an unstable cardiac conduction mechanism; minimal transient cyanosis; subnormal physique; low systolic blood pressure and narrow pulse pressure; and localized prominence of the left anterior chest wall in the region of the second, third, and fourth intercostal spaces.

The authors believe that uncomplicated cases of these two common congenital abnormalities can be diagnosed in a large percentage of the cases by observation of the features presented.

ZION.

Freeman, N. E., Leeds, F. H., and Gardner, R. E.: Sympathectomy for Obliterative Arterial Disease; Indications and Contraindications. Ann. Surg. **126**:873 (Dec.), 1947.

In the management of obliterative arterial disease of the extremities, sympathectomy has two functions: first, the abolishment of vasomotor tone and, second, the abetment of the collateral circulation. The authors point out that the greater the evidence of overactivity of the sympathetic nervous system, the better the results following sympathectomy. There are six guiding points which indicate an increase in vasomotor activity in an extremity: (1) coolness; (2) sweating, the combination making for a "cold, clammy foot or hand"; (3) cyanotic mottling of the digits; (4) constriction of the superficial veins; (5) delayed blanching of the extremity on elevation; and (6) the patient's subjective statement of improvement in the extremity following a paravertebral novocaine block.

In patients with obliterative arterial disease, whether it be due to thromboangiitis obliterans or to arteriosclerosis, if evidence of a high degree of vasomotor tone is present, then sympathectomy is indicated. Conversely, if little or no evidence of vasomotor activity is present, sympathectomy is not only useless but may actually prove to be harmful.

The authors cite Atlas' signs which contraindicate sympathectomy: (1) severe extensive arterial occlusion; (2) rapid blanching on elevation of the extremity; and (3) atrophy of skin and subcutaneous tissues. In addition to three cases reported by Atlas, the authors report four patients who were made worse by sympathectomy. All had evidence of low vascular tone and should not have been subjected to the operation.

The explanation of these observations lies in the fact that there is a dual anatomic structure in the peripheral circulation. First, there is the arteriovenous anastomosis in the form of the neuromyoarterial glomus, and second, the nutrient capillaries. The former is under the control of the sympathetic nervous system and is important in conservation and release of heat as well as serving as important shunts between the arterial and venous systems. When there is extensive arterial obliterative disease, sympathectomy opens these glomus shunts and indirectly interferes with the circulation through the capillaries, with consequent gangrene of an extremity in some cases.

LORD.

Cabrera, E., and Sodi-Pallares, D.: Discussion of the Circus Movement. Proof of Its Occurrence in the Clinical Auricular Flutter. Arch. inst. cardiol. de Mexico **17**:850 (Dec.), 1947.

The authors have studied the characteristics and possible modifications of the circus movement in clinical auricular flutter. The following conclusions were reached:

1. Rotation of the instantaneous axis is not in favor of a circus movement in auricular flutter; it is only evidence of the curve described by the vectocardiogram of the flutter which is also present in other cyclic electrical phenomena.

2. Intravenous injection of acetylcholine causes the acceleration of both the auricular and the ventricular rates. This can be used in the differential diagnosis between auricular flutter and auricular tachycardia because in the latter, acetylcholine either ends the attack or has no effect.

3. Intravenous injection of a large dose of acetylcholine in cases of flutter has never caused an auricular rate similar to that observed in auricular fibrillation, and no irregularity of the auricular waves was observed.

4. The acceleration of flutter caused by acetylcholine supports the theory of a circus movement.

5. The time of activation of the auricles was further studied by simultaneous tracings of esophageal and precordial leads. While the ventral aspect of the auricular mass was activated from above downward, the dorsal aspect was activated from below upward. This is in favor of the existence of a circus movement.

6. Rotation of the instantaneous axis and the auricular vectocardiogram suggested in all cases of flutter, except one, that the wave of activation was descending in the anterior part and ascending in the posterior part of the ventricular mass.

7. The rotation plane of the auricular vectocardiogram was further found in agreement with the hypothesis of a circus movement around the orifices of both venae cavae.

LUISADA.

Alzamora Castro, V.: Contribution to the Study of S-T Changes, Angina Pectoris and Subendocardic Infarctions. Arch. inst. cardiol. de Mexico **17**:870 (Dec.), 1947.

The authors describe in detail the anatomic, clinical, and electrocardiographic characteristics of a case with extensive subendocardial infarction involving the entire left ventricle and part of the right ventricle. The patient had repeated and almost continuous attacks of precordial pain during which the electrocardiogram showed downward displacement of the S-T interval in leads where the exploring electrode was near the epicardial surface, and upward displacement in those leads which record the cavity potentials.

A clinical diagnosis of a subendocardial infarction was made. At necropsy the subendocardial necrosis was found to be secondary to partial obliteration of the orifices of both coronary arteries caused by syphilitic aortitis. It is not known why a total decrease of the coronary blood flow should cause a selective subendocardial damage. A hypothetical explanation, based on mechanical factors, is advanced by the authors. The electrocardiographic changes encountered during the attacks of angina pectoris are similar to those reported in the present case. During the pain, a metabolic disturbance, probably related to oxygen deficiency, seems to occur; this affects chiefly the deeper or subendocardial portions of the left ventricle and is accompanied by electrical forces which produce transient electrocardiographic changes. When the circulatory disturbance is severe, prolonged, or repeated, as in this patient, the alterations may reach the stage of necrosis (infarct).

Certain clinical syndromes simulating coronary occlusion present electrocardiographic changes similar to those recorded during the attacks of angina pectoris and are probably due to the same basic circulatory changes. These cases have been classified by the authors as "subendocardial infarcts" and are characterized electrocardiographically by more or less permanent modifications of the S-T interval.

LUISADA.

Hejtmancik, M. R., and Herrmann, G. R.: Paroxysmal Ventricular Tachycardia With Special Reference to Treatment. Texas State J. Med. **53**:505 (Dec.), 1947.

A series of twenty cases of paroxysmal ventricular tachycardia has been analyzed by the authors. The average age of the patients in the series was 52.8 years, the youngest being 18 and the oldest, 80 years of age. Coronary artery disease was present in 70 per cent of the cases. The rates of the tachycardia varied between 110 and 220, with an average of 170 per minute. No correlation was observed between heart rate and prognosis. Fifteen of the cases were associated with signs of congestive failure. Three patients showed cerebral manifestations; in two these were due to the tachycardia itself, and in one they were secondary to cerebral embolism. One of these had generalized convulsive seizures and another had attacks of syncope. Of two patients with apparently normal hearts, one complained of precordial burning and the other had no symptoms referable to the disorder.

In three of the four patients receiving no specific therapy, the disorder persisted until death. Ten of twelve cases reverted to a normal rhythm on quinidine, given orally; the amount required varied from 0.6 Gm. to 5.2 Gm. in twenty-four hours. In one patient with acute myocardial infarction, the rhythm was not abolished by 11.8 Gm. of quinidine, given orally, over a period of four days, and the patient died. The two patients with no demonstrable heart disease were successfully treated, one with small and one with large oral doses of quinidine. In one patient, whose tachycardia reverted to a normal rhythm with intravenous injection of 16 mg. of morphine, even small doses of quinidine were found to prolong the QRS complex more than 25 per cent.

After reversion of the tachycardia to a normal rhythm, twelve patients were maintained on quinidine sulfate, orally, in doses of from 0.6 to 1.0 Gm. daily. In ten cases paroxysmal ventricular tachycardia did not recur on this maintenance regime. However, four of these patients died within one week, in spite of the established and maintained normal rhythm.

Two patients, in critical condition following myocardial infarction, were given quinidine intravenously. One had not responded to intravenous dosages of morphine of 11, 11, and 32 mg., and oral quinidine totalling 2, 5, and 3.3 Gm. on three successive days. This patient reverted to normal rhythm after 1.7 Gm. of quinidine sulfate was given by slow intravenous drip. Another patient, who was admitted in shock, showed no change in rhythm after being given 0.6 Gm. of quinidine sulfate intravenously in 10 c.c. of distilled water and died in about one hour. One patient under treatment for subacute bacterial endocarditis was given 1.0 Gm. of quinidine sulfate intravenously in divided doses over a period of twelve hours, and then reverted to normal rhythm after 1.2 mg. of Cedilanid was administered intravenously. The intravenous injection of 16 mg. of morphine sulfate resulted in immediate cessation of the abnormal rhythm in one patient with myocardial infarction. In another patient, the ventricular tachycardia reverted to sinus rhythm on carotid sinus pressure six minutes after 45 mg. of morphine sulfate had been given intravenously, the disturbance having been unaffected previously by repeated carotid sinus stimulation and 32 mg. of morphine.

BELLET.

American Heart Association, Inc.

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1949 campaign in planning stage

Planning and organizational work on the Association's 1949 campaign has been started, under the active leadership of the new Chairman of the Board, A. W. Robertson, Chairman of the Westinghouse Electric Corporation. National Heart Week, which will be observed February 14 to 21, will highlight the educational and fund-raising drive.

Thomas I. Parkinson, President of the Equitable Life Assurance Society of America, has been named Chairman of the National Sponsors Committee, which will be composed of prominent leaders in all fields of endeavor. This committee will lend prestige to the campaign and inspire the widest public support.

A National Campaign Planning Committee also is being organized among influential and outstanding citizens who will be delegated with responsibility for the conduct of the campaign. They will be directed by a National Campaign Chairman, still to be selected.

Other national committees covering various fields of activity are being formed under the direction of E. J. Ade, who has been appointed Fund-Raising Director for the Association. Mr. Ade formerly was associated with the John Price Jones Corporation as technical director for many major war funds drives, including British War Relief, the Red Cross, USO, and War Bonds. The committees now in formation will include representatives of medical groups, corporations, foundations, women's organizations, labor unions, clubs, and the publicity, sports, and entertainment fields.

A field staff is being briefed to assist local affiliates in their organizational as well as fund-raising efforts. One of the major objectives during the coming year will be the formation of additional local heart associations.

As in the previous campaign, cooperation of national service groups, clubs, fraternal organizations, and trade associations will be sought in the development of local campaigns.

All local efforts will be supported by a nationwide program of radio, newspaper, and magazine publicity which is now being planned. New educational pamphlets and posters are being designed, and preparation is being made for wide distribution of the Plastic Heart collection bank.

Monsanto aids plastic heart production

The Monsanto Chemical Company has made an important contribution to the heart campaign by making a substantial reduction in the price of the Lustron plastic material which will be used in manufacturing the Plastic Heart collection banks. This will greatly reduce the unit cost of the Plastic Hearts, which have proved an extremely valuable device for canvassing as well as for collections in retail stores and other locations.

First research grant

The Association has made its first research grant, presenting $25,000 to the Szent Gyorgyi Research Foundation, Inc. The grant will aid studies in muscular contraction being conducted by Dr. Albert Szent Gyorgyi, Research Director of the Foundation, and his associates, at the Marine Biological Institute, Woods Hole, Mass.

The grant is the first in a series which the Association is undertaking as a result of this year's initial nationwide fund-raising campaign.

Dr. Szent Gyorgyi is a winner of the Nobel Prize in Physiology and Medicine. He came to the United States from Hungary in 1946 at the invitation of the Massachusetts Institute of Technology.

POLICIES TOWARD AFFILIATES IN NEW BOOKLET

Policies recently adopted by the Assembly of the Association indicating the nature of relationships with local affiliates have just been issued in booklet form. They are available on request to the Association. The policies cover standards for affiliation of local heart associations, financial relationships, organizational structure, research, relations with other voluntary agencies, and division of principal responsibilities between the national Association and its affiliates.

NATIONAL ADVISORY HEART COUNCIL

The new National Advisory Heart Council, authorized by the bill creating a National Heart Institute in the United States Public Health Service, held its inaugural meeting in Washington September 8. Medical members of the Council include C. A. Elvehjem, Ph.D., University of Wisconsin; Dr. Tinsley R. Harrison, Southwestern Medical College; Dr. T. Duckett Jones, Helen Hay Whitney Foundation; Dr. Irvine Page, Cleveland Clinic; Dr. B. O. Raulston, University of Southern California School of Medicine; and Dr. Paul D. White, Massachusetts General Hospital. Lay members include James S. Adams, businessman, New York; Maurice Goldblatt, merchant and philanthropist, Chicago; Mrs. Albert D. Lasker, leader in public health affairs, New York; E. B. MacNaughton, publisher, Portland, Ore.; Ernest Mahler, Wisconsin businessman; and Albert J. Wolfe, President of the Board, Touro Infirmary, New Orleans.

The Council is authorized to carry out the following specific functions:

A. To review research projects in the cardiovascular diseases, applications for grants-in-aid for heart disease research projects, and applications for grants for training, instruction, and traineeships in the heart field; and to certify approval to the Surgeon General of those projects or applications which it believes will make significant contributions to human knowledge of diseases of the heart or will best carry out the purposes of the Act.

B. To collect information on studies being carried on in this country or abroad on diseases of the heart and, with the approval of the Surgeon General, make this information available to physicians, scientists, public and private health and welfare organizations, and the general public.

C. To recommend to the Surgeon General acceptance of conditional gifts.

D. To advise, consult with, and make recommendations to the Surgeon General with respect to carrying out the Act's provisions.

REGISTRY OF CARDIOVASCULAR DISEASES

The American Heart Association has appropriated $2,500 toward the establishment of a Registry of Cardiovascular Diseases as a unit of the American Registry of Pathology, which is under the auspices of the National Research Council.

The Registry will be administered by the Scientific Director of the American Registry of Pathology with the assistance of a Committee on the Registry of Cardiovascular Diseases of the Association. The Committee, which is now being formed, will create and supervise the policies of the Registry so as to make it of greatest interest and usefulness to specialists in the subject. One of its first duties will be to advise on the preparation of an appropriate blank for submitting cases to the Registry.

The purpose of the Registry will be to collect and report on data and material from cases of all types of cardiovascular diseases, furnish consultation service, prepare teaching material, and pursue definitive studies.

Material sent to the Registry by physicians, hospitals, or other reliable sources may consist of fresh or fixed pathologic specimens, slides, roentgenograms, electrocardiograms, drawings,

case records, or other data. Fresh specimens should be submitted when possible to permit dissection and orientation, and they should be accompanied by complete relevant data.

All material and correspondence should be sent to the Director, Army Institute of Pathology, 7th Street and Independence Avenue, S. W., Washington 25, D. C.

Material collected will be studied by the staff of the Institute and by pathologists, cardiologists, or other specialists on a consultant basis to the Institute. Correlation between the clinical data available and the findings on pathologic study in the registries should be made by the Institute staff and the consultants. Reports of the clinico-pathologic correlations will be made to the contributors and will be used by the staff in selecting material for inclusion in an atlas on cardiovascular diseases, a loan collection of slides showing all types of cardiovascular diseases collected by the Registry, and in preparation of cases for loan to be used at clinico-pathologic conference.

The contributor does not lose control of registered cases incorporated into the Institute files. He is still privileged to report them independently and may have the assistance of the Institute in preparing his illustrations. Permission of the contributor is obtained before his case is used in a study.

AHA ANNUAL MEETING, JUNE 3-4

The next annual meeting of the Association will take place at the Chalfonte-Haddon Hall, Atlantic City, N. J., on June 3 and 4, 1949. The Scientific Sessions will be held in the Vernon and Garden Rooms which accommodate 1,000 persons. Reservations should be made by writing directly to the hotel, at the earliest possible date, stating the exact type of accommodation desired and definite dates of arrival and departure.

DR. ANTONIO BATTRO DIES

Dr. Antonio Battro, distinguished Argentine cardiologist who made important contributions to medicine, died on May 24. He was well known in the United States. For the past few years, he was chief of the Department of Cardiology of the Institute de Investigaciones Fisicas Aplicadas a la Patologia Humana. Dr. Battro is the author of numerous scientific publications and the winner of many awards. In Argentina, he received the Luis Guemes Prize in 1928 and 1938, and the Premio Nacional de Ciencias in 1930.

DR. ERNSTENE HEADS MEDICAL DEPARTMENT

Dr. A. Carlton Ernestene has been appointed head of the Division of Medicine at the Cleveland Clinic. Dr. Ernstene joined the Clinic Staff in 1932 and has been head of the Section on Cardiovascular Disease for many years. He recently was elected president of the Cleveland Cardiovascular Society.